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243

Xiao Tan

# Effects of Exercise and Diet on Sleep Among Overweight and Obese Men With Chronic Insomnia Symptoms

JYVÄSKYLÄN YLIOPISTO

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Editors
Ina Tarkka
Faculty of Sport and Health Sciences, University of Jyväskylä
Pekka Olsbo
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## ABSTRACT

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Chronic insomnia symptoms are prevalent among adults. Current treatment strategies for chronic insomnia are restricted by shortcomings such as the side effects of pharmaceutical treatments, and high economic cost of cognitive behavioral treatment. Thus alternative methods for mitigating insomnia symptoms are needed. Accumulating evidence suggests that lifestyle factors, such as sedentary behavior and unbalanced diet are associated with sleep and/or insomnia symptoms. However, there is a lack of studies focusing on the overweight insomniac population, and randomized controlled trials concerning the effects of exercise and diet on insomnia symptoms are scarce.

In the present study, we aimed to investigate behavioral factors that are related to chronic insomnia symptoms among overweight and obese men. The effects of aerobic exercise and diet intervention on sleep among this population were also studied. The results showed that low level of leisure-time physical activity and high consumption of saturated fatty acid were independently associated with chronic insomnia symptoms. Six months of regular aerobic exercise training tailored by fitness level improved sleep in insomniacs by curtailing the objectively measured sleep onset latency and reducing the frequency of difficulty falling asleep. Moreover, a 6-month diet intervention also shortened the objective sleep onset latency in this population. This work highlights the associations between obesity-related lifestyle factors and chronic insomnia symptoms. Furthermore, by showing their effects on improving sleep, the study suggests a possibility of including exercise and diet intervention in the treatment strategies of chronic insomnia among overweight and obese men.

Keywords: Chronic insomnia symptoms, obesity, overweight, exercise, diet, sleep onset, males

**Author's address** Xiao Tan, MSc
Department of Health Sciences
University of Jyväskylä
FI-40014 Jyväskylä
Finland
tanxiao0529@gmail.com

**Supervisors** Professor Sulin Cheng, PhD
Department of Health Sciences
University of Jyväskylä
Jyväskylä, Finland

Professor Markku Partinen, MD, PhD
VitalMed Research Center
Helsinki Sleep Clinic
Helsinki, Finland

Docent Ina M. Tarkka, PhD
Department of Health Sciences
University of Jyväskylä
Jyväskylä, Finland

Professor Fengyu Cong, PhD
Department of Biomedical Engineering
Dalian University of Technology
Dalian, China

**Reviewers** Professor Dieter Riemann, PhD
Department of Psychiatry & Psychotherapy
Freiburg University Medical Center
Freiburg, Germany

Docent Katriina Kukkonen-Harjula, MD, PhD
Department of Rehabilitation
South Karelia Health and Social Care District (Eksote)
Lappeenranta, Finland

**Opponent** Docent Henri Tuomilehto, MD, PhD
Oivauni Oy
Kuopio , Finland

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## LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which will be referred to in the text by their Roman numerals.

I Tan X, Saarinen A, Mikkola TM, Tenhunen J, Martinmäki S, Rahikainen A, Cheng S, Eklund N, Pekkala S, Wiklund P, Munukka E, Wen X, Cong F, Wang X, Zhang Y, Tarkka IM, Sun Y, Partinen M, Alén M, Cheng S. Effects of exercise and diet interventions on obesity-related sleep disorders in men: study protocol for a randomized controlled trial. Trials. 2013; 14: 235.

II Tan X, Alén M, Cheng SM, Mikkola TM, Tenhunen J, Lyytikäinen A, Wiklund P, Cong F, Saarinen A, Tarkka IM, Partinen M, Cheng S. Associations of disordered sleep with body fat distribution, physical activity and diet among overweight middle-aged men. Journal of Sleep Research 2015; 24: 414-24.

III Tan X, Alén M, Wiklund P, Partinen M, Cheng S. Effects of aerobic exercise on home-based sleep among overweight and obese men with chronic insomnia symptoms: a randomized controlled trial. Sleep Medicine 2016, in press.

IV Tan X, Alén M, Wang K, Tenhunen J, Wiklund P, Partinen M, Cheng S. The effects of 6-month diet intervention on sleep among overweight and obese men with chronic insomnia symptoms: a randomized-controlled trial. Submitted for publication.

## ABBREVIATIONS

| | |
|---|---|
| AHI | Apnea-hypopnea index |
| ANOVA | Analysis of variance |
| ANCOVA | Analysis of covariance |
| BMI | Body mass index |
| BNSQ | Basic Nordic sleep questionnaire |
| CBT | Cognitive behavioral treatment |
| CBT-I | Cognitive behavioral treatment for insomnia |
| COM | Comorbid insomnia symptoms and obstructive sleep apnea |
| DIS | Difficulty initiating sleep |
| DMS | Difficulty maintaining sleep |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DXA | Dual-energy x-ray absorptiometry |
| EEG | Electroencephalogram |
| EMA | Early-morning awakenings |
| EMG | Electromyography |
| ESS | Epworth Sleepiness Scale |
| HNW | Normal weight and healthy without sleep disorders |
| HOW | Overweight without sleep disorders |
| ICSD | International Classification of Sleep Disorders |
| INS | Chronic insomnia symptoms only |
| ISI | Insomnia severity index |
| LTPA | Leisure-time physical activity |
| MET | Metabolic equivalent |
| MOTOSD | Monitoring and treatment of obesity-related sleep disorders |
| NREM | Non-rapid eye movement |
| NRS | Non-restorative sleep |
| NWAK | Number of nocturnal awakenings |
| OSA | Obstructive sleep apnea |
| PSG | Polysomnography |
| PSQI | Pittsburgh sleep quality index |
| REM | Rapid eye movement |
| SE | Sleep efficiency |
| SFA | Saturated fatty acid |
| SOL | Sleep onset latency |
| SWS | Slow wave sleep |
| TST | Total sleep time |
| $VO_{2max}$ | Maximal oxygen uptake |
| WASO | Wake after sleep onset |

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ORIGINAL PUBLICATIONS

# 1 INTRODUCTION

Human beings spend approximately one-third of their lifetime in sleep. Insufficient sleep and impaired sleep quality caused by sleep disorders are risk factors for several pathologies such as dementia (Benedict et al., 2015), cardiovascular diseases (Cappuccio et al., 2011; Westerlund et al., 2013), stroke (Altman et al., 2012; Wu et al., 2014), and type 2 diabetes (Meisinger et al., 2005). Major disorders that impair sleep and quality of life in humans include chronic insomnia symptoms, sleep apnea (mainly obstructive sleep apnea, OSA), restless legs syndrome (RLS), narcolepsy, and rapid eye movement sleep (REM) behavior disorders (Colten et al., 2006). Among these sleep disorders, chronic insomnia symptoms have the highest prevalence in the general population (Ohayon, 2002; Heatley et al., 2013) and have resulted in tremendous economic costs in western countries (Schenck et al., 2003; Ford et al., 2014). For instance, the annual total costs related to insomnia in USA were between $92 to $107 billion USD in year 2010 (Rosekind et al., 2010), and the cost per untreated insomnia case in Canada was estimated at $5,000 CAD in year 2009 (Daley et al., 2009). In Finland, the estimated costs of insomnia are not known, but up to 28% of sickness absences are due to sleep disturbances (Lallukka et al., 2014).

Current treatments of chronic insomnia symptoms suffer from several disadvantages. Pharmacological therapies such as benzodiazepines and benzodiazepine-receptor agonists may result in a range of adverse reactions, such as disrupted circadian rhythm, daytime drowsiness, cognitive and psychomotor impairment, rebound insomnia, or withdrawal symptoms on discontinuation, and thus cannot be used continuously (Morin et al., 2007; Greenblatt & Roth, 2012). Behavioral therapy, such as cognitive behavioral treatment for insomnia (CBT-I), is verified as an effective long-term treatment of choice for chronic insomnia (Edinger et al., 2001; Morin et al., 2009). However, in comparison with the very large insomniac population, limited treatment resources such as the number of therapists significantly restrict CBT-I's

availability (Espie et al., 2012). Hence, there is an urgent need for alternative treatments for insomnia.

The existence of a relationship between obesity and chronic insomnia symptoms has been recognized and studied during recent years. Insomnia per se has been found to be associated with overweight among middle-aged to older men (Janson et al., 2001). Another population-based study revealed an association between increased body mass index (BMI) and higher risk for insomnia over a 10- to 13-year follow-up (Palm et al., 2015). Taking into consideration the prevalence of overweight/obesity in developed and many developing countries (James, 2004), the number of overweight subjects with chronic insomnia symptoms is likely to be tremendous. Nevertheless, few studies have investigated insomnia symptoms solely among overweight or obese individuals, and hence potential factors associated with insomnia symptoms in this population remain unclear.

Sedentary behavior such as low level of physical activity is a major risk factor for obesity (Mozaffarian et al., 2011). In addition, insomnia is independently associated with lack of physical activity (Janson et al., 2001; Haario et al., 2013). Another cohort study has shown that women with better sleep quality engage in a higher amount of habitual exercise compared to their counterparts with worse sleep quality (Kline et al., 2013). Hence overweight insomniacs encouraged to undertake a certain amount of regular exercise may mitigate their symptoms. Previous interventional studies reported that aerobic exercise training is an effective way to improve sleep quality among patients with chronic insomnia or chronic sleep complaints (King et al., 2008; Reid et al., 2010; Passos et al., 2011). However, measurements of obesity/overweight were not included in these studies, thus the associations between overweight, chronic insomnia symptoms, and exercise are yet to be studied through interventional trials.

Diet is another important mediator between sleep and overweight. Experimental studies found that sleep restriction could result in higher energy intake (St-Onge et al., 2011), and weight gain (Spaeth et al., 2013) among healthy adults. On the other hand, growing evidence suggests that diet changes may directly influence sleep. Short-term diet alterations in normal sleepers (sleep 7 – 9 h/night) showed that greater fiber intake contributed to better objective sleep quality, such as longer slow wave sleep, whereas high saturated fat and sugar intakes led to the contrary result (St Onge et al., 2015). In addition, although the causal relationships were not established, population-based studies found that nutrient intakes were associated with insomnia symptoms (Grander et al., 2014; Kurotani et al., 2015). However, to date, whether a long-term dietary intervention by optimizing diet composition and reducing total energy intake could improve sleep among insomniacs has not been investigated. There is also a lack of information about the effects of

diet-induced weight control on sleep quality among overweight adults with insomnia symptoms.

Therefore, the present study aimed to investigate the behavioral factors related to chronic insomnia symptoms in overweight men. The study also tested the efficacy of long-term individualized exercise or diet intervention in improving sleep among overweight men with chronic insomnia symptoms. The results of this study will not only deepen our understanding about the associations between overweight, physical activity, diet, and insomnia symptoms, but also shed light on lifestyle intervention methods for treating insomnia.

# 2 REVIEW OF THE LITERATURE

## 2.1 Classification criteria of chronic insomnia symptoms

Insomnia is a patient-reported sleep disorder in which there is difficulty initiating and/or maintaining sleep despite adequate sleep opportunity. In addition, depending on the classification criteria, non-restorative sleep may also be regarded as a symptom of insomnia. The duration of insomnia symptoms ranges from days to years, and insomnia is generally considered to be chronic when the relevant symptoms last for one month or longer (Rajput & Bromley, 1999). However, amongst a considerable proportion of individuals with insomnia, the symptoms persist for a longer period, and can repeatedly occur during the lifespan (Buysse, 2008).

Symptoms of chronic insomnia can be either independent or dependent of a medical, psychiatric, or environmental cause. The criteria for insomnia diagnosis have, until recently, been based on distinguishing insomnia disorders according to their presumed pathophysiology, and attributing the insomnia not caused by other symptoms as primary (American Psychiatric Association, 2000; American Academy of Sleep Medicine, 2005). However, this has been challenged in clinical practice in recent years, because the majority of insomnia conditions share numerous characteristics in primary or secondary insomnia, and an emphasis on the "secondary" nature of many insomnia disorders could result in inadequate treatment (Sateia, 2014). Hence, in the recent update of the two commonly used criteria: the International Classification of Sleep Disorders – Third Edition (ICSD-3), and the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5), classification of (chronic) insomnia disorder no longer emphasizes its primary or secondary status (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013).

The full diagnostic criteria for chronic insomnia disorder according to ICSD-3 includes: 1) A report of difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), early morning awakenings (EMA), or sleep that is chronically non-restorative or poor in quality (NRS). The difficulty occurs at least 3 nights per week and lasted for 3 months or longer; 2) The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep; 3) At least 1 of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient: fatigue or malaise; attention, concentration, or memory impairment; social or vocational dysfunction or poor school performance; mood disturbance or irritability; daytime sleepiness; motivation, energy, or initiative reduction; proneness for errors or accidents at work or while driving; tension, headaches, or gastrointestinal symptoms in response to sleep loss; concerns or worries about sleep (American Academy of Sleep Medicine, 2014).

In DSM-5, (chronic) insomnia disorder is classified as: 1) Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), early-morning awakenings (EMA); 2) The sleep disturbance causes significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning; 3) The sleep difficulty occurs at least 3 nights per week, is present for at least 3 months, and despite adequate opportunity for sleep; 4) The insomnia does not co-occur with another sleep disorder; 5) The insomnia is not explained by coexisting mental disorders or medical conditions (American Psychiatric Association, 2013).

The vast majority of the current literature is based on the ICSD-2 (American Academy of Sleep Medicine, 2005), or the DSM-IV-TR (American Psychiatric Association, 2000) criteria for (primary) insomnia. Regarding the definition of insomnia and its symptoms, both ICSD-2 and DSM-IV-TR criteria are mostly congruent with the updated version. The major difference in ICSD-2 compared to ICSD-3 criteria is the absence of reference to the frequency and duration of insomnia symptoms. Moreover, non-restorative sleep is removed from the list of insomnia symptoms in DSM-5 compared to its earlier version, and the symptom duration criterion is extended from one to three months (American Psychiatric Association, 2013; Riemann et al., 2015).

## 2.2 Prevalence of chronic insomnia symptoms

Epidemiological studies have estimated prevalence of insomnia symptoms according to different classification levels as follows: 1) any insomnia symptom without restriction criteria; 2) chronic insomnia symptoms with frequency and

duration; 3) chronic insomnia symptoms with frequency, duration, and daytime consequences. The prevalence of insomnia symptoms among the general population varies from 30-65.4% by Level 1 (Ohayon, 2002; Chung et al., 2015), to 16-42.0% by Level 2 (Ohayon, 2002; Ohayon & Reynolds, 2009; Chung et al., 2015), and narrows to 15.1-22.1%, by Level 3 (Roth et al., 2011; Pallesen et al., 2014; Chung et al., 2015). Among Finnish adults, the recent prevalence of insomnia symptoms by categories 1 and 2 was comparable to that of other developed countries (Lallukka et al., 2010). However, a previous study reported that prevalence of full-diagnosed chronic insomnia (DSM-IV criteria) in Finland was 1.5-2 times higher than non-Nordic European countries (Ohayon & Partinen, 2002).

Symptoms of chronic insomnia can exclusively exist or can coexist with each other in individuals. The prevalence of insomnia symptoms among adults in different age groups is as follows: 6.7-22.8% for difficulty initiating sleep (DIS); 5.6-33.3% for difficulty maintaining sleep (DMS); 3.1-22.8% for early morning awakenings (EMA); and 8.7-17.8% for non-restorative sleep (NRS, Ohayon & Reynolds, 2009; Pallesen et al., 2014). In general, DMS is the most prevalent insomnia symptom among adults. Prevalence of DIS, DMS, and EMA increases with age, while occurrences of NRS are evenly distributed across age groups (Ohayon & Reynolds, 2009).

## 2.3 Assessment of sleep quality in individuals with chronic insomnia symptoms

### 2.3.1 Subjective measurements

Subjective complaints about sleep are usually considered as the primary outcomes of insomnia. Current studies regarding populations with chronic insomnia symptoms use different instruments for assessing subjective sleep quality. These include sleep diaries and various scales and questionnaires.

Sleep diaries are widely used to collect subjective sleep data. The diary is usually completed consecutively over at least seven nights. A sleep diary with instruction is delivered to the subject before the first assessment night. Subjects are often instructed to fill in the time going to bed, estimated time of falling asleep, waking-up time in the morning, and number of awakenings during the night (Carney et al., 2012). Total awaken time during the night, total sleep time, and other related issues may also be asked. Therefore, sleep parameters such as sleep onset latency (SOL), number of nocturnal awakenings (NWAK), as well as total sleep time (TST), wake after sleep onset (WASO), and sleep efficiency (TST/Total time in bed, SE) can be determined.

The Pittsburgh sleep quality index (PSQI) is the most commonly used questionnaire for assessing sleep quality and disturbances. The PSQI includes 19 items, which generate the following seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Buysse et al., 1989). PSQI is determined as a global score as the sum of all items. In addition, the sub-score of each component can be used in assessing related insomnia symptoms or sleep disorders. The recall period of PSQI is the past month.

The Insomnia severity index (ISI) is another questionnaire-derived index which is designed as an instrument for measuring subjective perception of insomnia. ISI includes seven questions concerning insomnia symptoms, sleep satisfaction, and consequences of insomnia on daytime functions. The total score is counted for classification of insomnia severity (Morin, 1993). Unlike PSQI, ISI focuses on the severity level rather than frequency of insomnia symptoms. ISI reflects current condition (i.e. the last two weeks).

The Basic Nordic sleep questionnaire (BNSQ) has been developed as a standardized sleep questionnaire that can be used as a basis for questionnaires (Partinen & Gislason, 1995). BNSQ includes questions regarding insomnia symptoms, daytime sleepiness, chronotype, sleep breathing, sleep duration, nap, etc. It introduces a 1-5 scale for measuring frequency of insomnia symptoms, as follows: 1) never or less than once per month; 2) less than once per week; 3) on 1-2 nights per week; 4) on 3-5 nights per week; 5) every night or almost every night. BNSQ recalls conditions during the past three months.

In addition, there are other commonly used questionnaires for evaluating daytime sleep-related outcomes, such as Epworth Sleepiness Scale (ESS) and Stanford Sleepiness Scale. Such questionnaires can be used among insomniacs however, not as main endpoints.

### 2.3.2 Objective measurements

Polysomnography (PSG) is the current gold standard for objective sleep measurement (Blackwell et al., 2008; Marino et al., 2013). However, the cost of measurement, conditions of measurement preparation and environment, and potential discomfort due to restricted bodily movement all significantly limit the utility of PSG in sleep measurement among the insomniac population. Insomnia studies that implement PSG measurements may encounter the shortcoming of a limited number of measurement nights (Passos et al., 2011), which enhances measurement bias due to night-to-night variability of sleep parameters among insomniacs (Edinger et al., 1991). Hence, approaches of measuring objective sleep out of laboratory environment are required in research.

Sleep is accompanied with significantly reduced limb movements (Marino et al., 2013). Using movement data to infer sleep or wake status has been increasingly accepted into practice during the past decades (Marino et al., 2013). Wrist actigraphy is a device that consecutively measures upper limb movements (acceleration). The acceleration data are saved in the device memory, and can be read using software with algorithms for distinguishing sleep or wake status (Hauri & Wisbey, 1992). Due to its feasibility in large-scale and long-term measurements, wrist actigraphy is recommended as the optimal instrument for measuring objective sleep parameters among the insomniac population (Hauri & Wisbey, 1992). The validity of wrist actigraphy in detecting sleep/wake among insomniacs has been tested against PSG in various studies (Lichstein et al., 2006; Marino et al., 2013). In these studies, Lichstein et al. compared actigraphy (actigraphy device: AW-64, Minimitter Inc, OR, USA; algorithm: Actiware Sleep v. 3.3) and PSG-determined TST, SOL, WASO, SE, and NWAK, and found satisfactory correlations for all parameters except SOL (Lichstein et al., 2006). Marino et al. carried out another validation (actigraphy device: AW-64, Minimitter Inc, OR, USA and Actiwatch Spectrum, Philips/Respironics, Murrysville, PA, USA; algorithm: Cole-Krinpke) against PSG among a mixed population of insomniacs and normal sleepers. Actigraphy-measured sleep/wake data were found to have high accuracy (0.863, proportion of 30-s sleep epochs consistent with PSG in all total duration), high sensitivity (0.965, ability to correctly identify sleep), but low specificity (0.329, ability to correctly identify wake) (Marino et al., 2013).

It is worth noting that technologies with potential uses in long-term sleep measurement have been developing fast in recent years. Non-invasive sleep measurement based on piezoelectric devices could find wide application in home-based sleep screening among patients with chronic insomnia or other sleep disorders such as OSA and RLS. Piezoelectric sensor measures the electric change in response to applied mechanical stress (Mang et al., 2014). An important advantage of such sensors over actigraphy is that they can detect not only locomotor activities, but also more subtle movements such as respiration (thorax movement) and heart beat (ballistocardiography) (Shin et al., 2010). According to the known alterations of respiration rhythm and heart rate between sleep and wake (Pivik & Busby 1996; Farina et al., 2014; Long et al., 2015), distinguishing sleep or wake with better accuracy than actigraphy appears feasible. Initial validation of a piezoelectric device (Beddit pro, Beddit Ltd., Espoo, Finland) against PSG (n = 40) in determining respiration and heart rate showed high accuracy (Paalasmaa et al., 2012). However, validation of the algorithm for distinguishing sleep/wake based on heart rate, respiration, and bodily movement needs to be carried out among different populations.

## 2.4 Behavioral risk factors of chronic insomnia symptoms

### 2.4.1 Overweight and obesity

Overweight (Body mass index, BMI ≥ 25 kg $m^{-2}$) and obesity (BMI ≥ 30 kg $m^{-2}$) are widely considered to be associated with short sleep duration (Cappuccio et al., 2008) and sleep disorders such as OSA (Romero-Corral et al., 2010) and RLS (Gao et al., 2009). In addition, a number of studies have also investigated whether there is a link between overweight and insomnia symptoms (Fogelholm et al., 2007; Crönlein et al., 2015; Palm et al., 2015). One population-based study reported that sleep-related disturbances are associated with obesity (determined by BMI or waist circumference), and that the associations are independent of OSA (Fogelholm et al., 2007). Further, a recent study on college students revealed a negative correlation between fat mass and actigraphy-determined sleep efficiency (SE) in men (Kahlhöfer et al., 2016). Although insomnia symptoms were not specifically measured in these studies, the results suggest that there is likely to be a relationship between overweight and insomnia symptoms.

Recently, a population-based longitudinal study further implied the association between overweight and insomnia symptoms by showing that adults with higher BMI had more insomnia-related sleep problems (Palm et al., 2015). Moreover, the study also reported that during a 10-13-year follow-up, those with greater BMI increase had a higher risk of developing difficulty of maintaining sleep (DMS) and excessive daytime sleepiness (Palm et al., 2015). This indicates that weight gain may lead to insomnia symptoms. Nevertheless, the results of another study challenged the association between overweight and insomnia by showing that patients with diagnosed chronic primary insomnia from a random sample did not have higher BMI than healthy counterparts (Crönlein et al., 2015).

### 2.4.2 Low level of physical activity

Physical activity has long been associated with better sleep. Accumulating evidence suggests that low level of physical activity is a risk factor for insomnia symptoms in various populations (Janson et al., 2001; Smagula et al., 2016). Cross-sectional data from a Finnish population showed that, compared to those with higher level of physical activity, adults who were physically inactive (physical activity of less than 14 MET hours per week) had insomnia symptoms more frequently (Haario et al., 2013).

Being physically active is associated with reduced risk of suffering chronic insomnia symptoms. Among middle-aged women, consistently high exercise

activity level is associated with better sleep quality in terms of higher PSG measured SE and higher PSQI scores (Kline et al., 2013). Among men, regular participation in both light and strenuous physical activity is associated with lower risk of tiredness upon awake (Fabsitz et al., 1997). Sherrill et al. found that both men and women had significantly reduced risk of disorders of maintaining sleep if they were having regular physical activity at least once a week, participating regularly in an exercise programme, or walking at a normal pace for more than 6 blocks per day (Sherrill et al., 1998). Further, older adults engaging in higher levels of leisure time physical activity had a lower prevalence of difficulty initiating sleep, and the association was independent of major covariates such as BMI, gender, and age (Kitano et al., 2014).

The link between physical activity and chronic insomnia symptoms is likely to be bi-directional. Recent research has emphasized that poor sleep discourages people from being physically active during the day, possibly due to tiredness and sleepiness (Kline 2014). Studies showed that sleep parameters (subjective sleep quality, subjective SOL, objective SE) predict physical activity behavior on the following day (Dzierzewski et al., 2014; Baron et al., 2013; Lambiase et al., 2013). In the long-term, a 7-year follow-up study found that insomnia symptoms were associated with a physically inactive lifestyle at follow-up after adjustment for gender, age, and other corresponding unhealthy behavior at baseline (Haario et al., 2013). It has been proposed that improving sleep quality may contribute to higher levels of daytime physical activity (Kline et al., 2014). However, a study of older insomnia patients rebutted this notion by revealing that low physical activity level persists despite the improvement in sleep achieved through a 4-week behavioral treatment (Kline et al., 2014). Hence, to first motivate individuals with chronic insomnia symptoms engaging in regular physical activity is the key to improving their sleep.

### 2.4.3 Dietary and nutritional factors

Taking into account the associations between insomnia symptoms, overweight, and physical activity, diet is potentially another important mediator in this respect. Numerous studies have suggested that restricted or deprived sleep leads to higher energy intake, which may further predispose to overweight/obesity (St-Onge, 2013). On the other hand, studies have found that dietary alteration, especially adjustment of energy-yielding nutrients, also influences sleep (Phillips et al., 1975; Wells et al., 1997; St-Onge et al., 2016). Therefore, similar to the association between physical activity and sleep, a reciprocal relationship may exist between diet and sleep.

Cross-sectional and interventional studies have revealed that several dietary factors are related to insomnia symptoms. These factors concern dietary pattern, certain food items, macro- and micronutrients. A population based

study among adults aged 18-70 years showed that a diet high in vegetables, soy, and eggs was associated with less difficulty initiating sleep (Kurotani et al., 2015). Kitano et al. reported that in older adults, higher consumption of milk products is independently associated with lower prevalence of difficulty initiating sleep (Kitano et al., 2014). Moreover, placebo controlled, double blind studies have tested the efficacy of certain food products in improving sleep. One study aimed on older adults with chronic insomnia showed that, compared to the placebo period, a 2-week intake of tart cherry juice blend reduced WASO assessed by 2-week sleep diary (Pigeon et al., 2010). Another study reported that among older adults, actigraphy-determined SE and NWAKs were reduced after a 3-week intake of 100 g *Lactobacillus helveticus* fermented milk per day, compared to the placebo period (Yamamura et al., 2009).

Population based studies have discovered the associations between energy-yielding nutrients and insomnia symptoms. Among 4435 Japanese non-shift workers, low protein intake (<16% vs ≥16% of total energy) was associated with DIS and poor subjective quality of sleep, high protein intake (≥19% vs <19 of total energy) with DMS, and low carbohydrate intake (<50% vs ≥50% of total energy) with DMS (Takana et al., 2013). Grandner et al. reported that the odd ratios of insomnia-related sleep symptoms were associated with nutrient intakes based on 4552 US adults, and the prevalence of DMS was found to be negatively correlated with carbohydrate intake (Grandner et al., 2014). In non-energy-yielding nutrients, low dietary fiber intake was associated with the prevalence of self-reported sleep symptoms (Grandner et al., 2014) and the impaired objective sleep quality (St-Onge et al., 2016).

Micronutrients also play a role in sleep regulation and are linked to insomnia symptoms. Population-based data have indicated that less dietary vitamin D intake is related to a higher prevalence of DMS (Grandner et al., 2014). This finding is further supported by another study which showed that lower levels of serum vitamin D are associated with poorer objectively measured sleep including shorter TST and lower SE (Massa et al., 2015). Furthermore, population-based data suggested independent associations between DIS and lower intakes of selenium and calcium, and between NRS and lower intakes of vitamin C and calcium, respectively (Grandner et al., 2014). Interventional studies have also unveiled an association between insomnia symptoms and intakes of certain micronutrients. A double-blind placebo controlled trial reported that magnesium and zinc supplements accompanied with melatonin improved sleep quality among older adults with chronic insomnia (Rondanelli et al., 2011). However, whether the improvement was independent of melatonin intake was not mentioned.

In summary, information regarding nutritional intakes and chronic insomnia symptoms is fragmentary. Associations between energy-yielding

nutrients, non-energy-yielding macronutrients, micronutrients and occurrence of insomnia symptoms need to be systematically studied in order to strengthen the knowledge base of this topic.

### 2.4.4 Other behavioral risk factors

Alcohol intake and smoking are among the behavioral factors related to chronic insomnia symptoms. The association between higher alcohol consumption and insomnia or its related sleep complaints has been found among people of working age (Tachibana et al., 1996; Härmä et al., 1998). Furthermore, the prevalence of insomnia is high among people with alcohol use disorder (Brower, 2015). Smoking is suggested as another risk factor of insomnia symptoms. A cross-sectional study between smokers (median smoking history 13.1 years, mean consumption 21.2 cigarettes per day) and non-smokers found more insomnia-like sleep impairments in the former group (Jaehne et al., 2012). Other factors that may disrupt sleep quality, such as caffeine intake, have yet to be shown to have a direct association with chronic insomnia symptoms (Clark & Landolt, 2016).

## 2.5 Exercise training as a treatment alternative for chronic insomnia symptoms

Currently, cognitive behavioral treatment (CBT) is the primary non-drug treatment recommended by healthcare guidelines for chronic insomnia symptoms (Buysse 2013; Winkelman 2015). In addition to the CBT, exercise has been suggested as a potential non-drug treatment alternative for chronic insomnia (Youngstedt, 2005), based on several reasons. First, evidence shows that people with higher levels of habitual physical activity have lower risks of prevalence, persistence, and late-life incidence of insomnia (Morgan, 2003). Second, by increasing energy expenditure and elevating body temperature, exercise stimulates energy conservation and down-regulation of body temperature, which agrees with current hypotheses of the mechanisms underlying the wake-sleep transition (Horne & Staff 1983; Berger & Phillips, 1995). Moreover, compared to CBT, exercise provides a cost-effective way for long-term health care in individuals with chronic insomnia symptoms (Youngstedt, 2005).

### 2.5.1 Type and intensity of acute exercise for mitigating insomnia symptoms

A limited number of studies have aimed to investigate the effects of different exercise types and intensity levels on sleep among individuals with chronic insomnia symptoms. In one study, acute exercise interventions were implemented respectively as: 1) moderate-intensity aerobic exercise (50 mins continuous treadmill exercise on the level of first ventilatory threshold), 2) high-intensity aerobic exercise (three periods of 10 mins treadmill exercise on the level of second ventilatory threshold, with 10 mins rest between each two periods), and 3) moderate-intensity resistance exercise (three sets by ten repetitions at 50% of one repetition maximum on different muscle groups; Passos et al., 2010). Sleep was measured by both overnight PSG and daily sleep log. Subjects undertaking moderate-intensity aerobic exercise, but not other type/level of exercise showed improvement in objective and subjective sleep parameters following exercise (Passos et al., 2010).

### 2.5.2 Effects of long-term aerobic exercise training on chronic insomnia symptoms

The majority of studies under this topic have implemented long-term (one month or longer) exercise training among individuals with chronic insomnia symptoms. Two systematic reviews have summarized the effects of exercise training on sleep among adults with insomnia symptoms or sleep disturbances, indicating a positive effect of exercise on improving sleep parameters (Yang et al., 2012; Kredlow et al., 2015). Here we reviewed up to date randomized studies regarding the influences of aerobic exercise training on sleep (Table 1). In a randomized study dating from 1995, late afternoon moderate aerobic exercise was performed for four weeks among ten patients with chronic psychophysiologic insomnia. Improvement trends in SOL and NWAK were found after the exercise intervention, although without statistical significance (Guilleminault et al., 1995). Later, King et al. carried out two randomized-controlled studies among older adults with chronic insomnia-related sleep complaints (King et al., 1997; King et al., 2008). The first one implemented a 16-week, and the latter a 12-month aerobic exercise programme. In both studies, the exercisers improved self-rated sleep after intervention compared to the controls. In the latter study with 12-month intervention, objective sleep measurement (PSG) was included, and the results supported the positive effects of long-term aerobic exercise on sleep among older individuals (King et al., 2008).

In recent years, studies focused on patients with diagnosed chronic insomnia further identified the efficacy of long-term aerobic exercise in mitigating insomnia symptoms and improving sleep. Among middle to older

aged adults with chronic insomnia, a 16-week randomized aerobic exercise programme successfully improved subjective sleep quality assessed by global PSQI, SOL, sleep duration, SE, and daytime dysfunction, in comparison with the controls without exercise intervention (Reid et al., 2010). In another randomized study that implemented 6-month moderate aerobic exercise on sedentary individuals with chronic insomnia, both PSG and subjective sleep parameters improved through intervention. The improved PSG outcomes included decreased SOL, WASO, and increased SE. Subjective improvement was shown by sleep-diary assessed SOL, sleep quality, and feeling rested in the morning (Passos et al., 2011). A recent study has tested whether long-term physical activity at internationally recommended minimum levels could improve sleep quality among chronic insomnia patients. Participants walked for 150min/wk at moderate intensity, and after the 6-month intervention, significantly reduced insomnia severity (assessed by the Insomnia Severity Index, ISI) was found among exercisers compared to the controls (Hartescu et al., 2015).

TABLE 1 Randomized studies investigating the effects of long-term aerobic exercise on sleep among individuals with chronic insomnia symptoms.

| Study | Participants | Exercise programme | Sleep outcomes |
|---|---|---|---|
| Guilleminault et al., 1995 | 30 adults with ⩾ 6 mo insomnia complaints and less than 6 h sleep per night, exercise + sleep hygiene (n = 10), light therapy + sleep hygiene (n = 10), sleep hygiene (n = 10) | 4-wk moderate aerobic exercise (walking) | **Sleep diary**: ↑ TST, ↓ SOL, ↓ NWAK, compared to baseline values, not significant |
| King et al., 1997 | 43 sedentary older adults (aged 50-76 yrs; women n = 29) with chronic moderate sleep complaints (⩾ 3 mo), exercise (n = 20), wait-listed control (n = 23) | 16-wk community-based low-impact aerobics and brisk walking, 30-40 min/session, 4 sessions/wk, at 60-75% estimated maxHR | ↓ **PSQI** global sleep score<br>**Sleep diary**: ↓ SOL, ↑ TST, compared to controls |
| King et al., 2008 | 66 older adults (aged ⩾ 55 yrs; women n = 44) with chronic mild-moderate sleep complaints (⩾ 3 mo), exercise (n = 36) health education control (n = 30) | 12-mo moderate endurance exercise in supervised class, 45min/class, 2 classes/wk, plus home-based exercise ⩾ 30 min/day, 3 days/wk, all exercise at 60-85% estimated maxHR | **PSG**: ↓ stage 1 duration, ↑ stage 2 duration, ↓ NWAK in first third of sleep period<br>↓ **PSQI** sleep disturbance subscale score<br>**Sleep diary**: ↓ SOL, ↑ rest-feeling in the morning, compared to controls |

| | | | |
|---|---|---|---|
| Reid et al., 2010 | 17 sedentary adults (aged ≥ 55 yrs; women n = 16) with chronic primary insomnia (≥ 3 mo), aerobic exercise plus sleep hygiene (n = 10), non-exercise plus sleep hygiene (n = 7) | 16-wk aerobic exercise by walking, stationary bicycle, or treadmill, 40 min/session, 4 sessions/wk, at 75% estimated maxHR (first 4-6 wk with lower intensity and shorter duration) | **PSQI**: ↓ global sleep score, ↓ sleep latency, ↓ sleep duration, ↓ daytime dysfunction, ↓ sleep efficiency sub-scores, compared to controls |
| Passos et al., 2011 | 19 sedentary adults (aged 30-55 yrs) with chronic primary insomnia (> 6 mo), morning exercise (n = 10), late-afternoon exercise (n = 9) | 6-mo group aerobic exercise on treadmill in exercise lab, 50 min/session, 3 sessions/wk, at treadmill speed relative to subject's first ventilatory threshold | **PSG**: ↓ SOL, ↓ WASO, ↑ SE<br>**Sleep diary**: ↓ SOL, ↑ sleep quality, ↑ rest-feeling in the morning, compared to baseline values, in both groups |
| Hartescu et al., 2015 | 41 adults with chronic (≥ 3 mo) insomnia (aged ≥ 40 yrs; women n = 30), exercise intervention (n = 20), control (n = 21) | 6-mo moderate-intensity exercise by brisk walking, 30 min/d, 5 d/wk | ↓ **ISI**, compared to controls |

↓ decreased value; ↑ increased value; RCT, randomized controlled trial; TST, total sleep time; SOL, sleep onset latency; NWAK, number of awakenings; maxHR, maximum heart rate; PSQI, Pittsburgh sleep quality index; PSG, polysomnography; SE, sleep efficiency; WASO, wakefulness after sleep onset; ISI, insomnia severity index.

## 2.6 Effects of diet intervention on sleep

Although no study has investigated whether diet intervention can improve sleep among individuals with chronic insomnia symptoms, growing evidence suggests that dietary factors may directly influence sleep (Perron et al., 2015; St-Onge et al., 2016). Dietary interventions by adjusting total energy intake, proportions of energy-yielding nutrients, or consumption of other nutrients have been carried out regarding their effects on sleep.

Regardless of obesity, energy balance (the difference between total energy intake and total energy consumption) is assumed to be a contributor of sleep/wake abnormalities (Perron et al., 2015), thus altering energy balance by changing total energy intake may influence sleep. Results of a recent animal study supported this hypothesis (Perron et al., 2015). In this study, one-week ad libitum feeding with increased energy density (high fat diet), resulted in

increased sleep/wake fragmentation in mice (determined by electroencephalogram and electromyography, EEG/EMG), which indicates an association between excessive total energy intake and worsened objective sleep quality. Human studies are clearly needed to investigate such potential influences between energy balance and sleep.

Sleep may also be acutely affected by adjusting the proportions of energy-yielding nutrients in the diet. Phillips et al. first highlighted the influences of daily diet on the following night's sleep, by carrying out a trial which compared sleep EEG following a 2-day high-carbohydrate, low-fat diet, a 2-day low-carbohydrate, high-fat diet, and a 2-day normal balanced diet in eight normal-weight men. Compared to the other diet patterns, decreased slow wave sleep (SWS) was shown for the high-carbohydrate, low-fat diet (Phillips et al., 1975). Another study reported that among healthy adults, self-reported sleepiness and fatigue were higher 2-3 hours after a high-fat-low-carbohydrate meal, compared to a low-fat-high-carbohydrate meal with an equivalent energy amount (Wells et al., 1997). Furthermore, a recent study on 26 normal sleepers compared nocturnal PSG parameters between days with a controlled diet (31% of energy from fat and 7.5% from saturated fat, 53% of energy from carbohydrates, 17% of energy from protein) and a day with an ad libitum diet (St-Onge et al., 2016). Less SWS and longer SOL were found following the ad libitum intake day, which was characterized by higher proportions of sugar and saturated fatty acids in energy-yielding nutrients. Nevertheless, it is not clear whether such sleep effects are due to changed energy balance, or alteration of proportions of energy-yielding nutrients, or both.

## 2.7 Mechanisms underlying behavioral factors and chronic insomnia symptoms

The mechanisms underlying chronic insomnia symptoms and behavioral factors such as physical activity, diet, and overweight largely remain to be studied. Several hypotheses have been proposed. Homeostasis, which involves both energy balance and thermoregulation, is a pivotal mediator between the behavioral factors and chronic insomnia symptoms. Furthermore, alterations of appetite- and sleep-related hormone levels represent the basis of the behavior-homeostasis-insomnia association. The proposed mechanisms discussed in this dissertation are shown in Figure1.

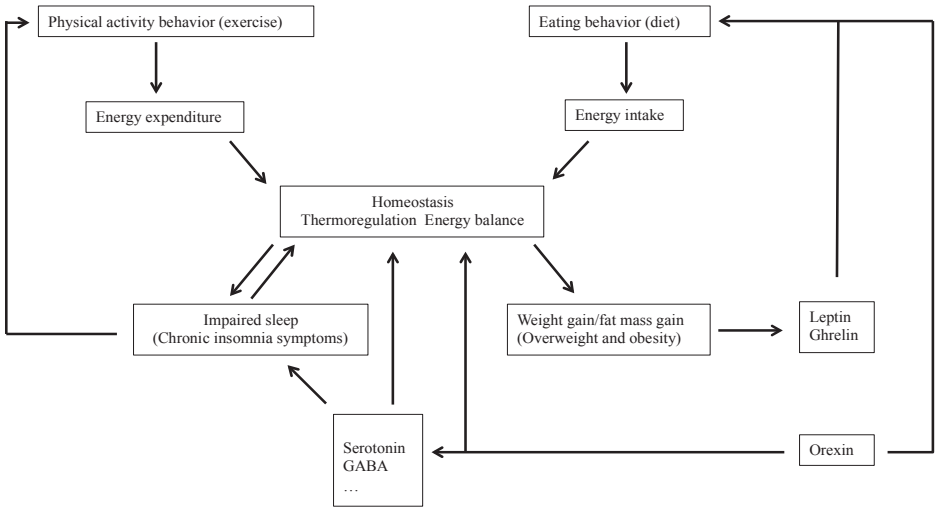



FIGURE 1 Association pathways regarding exercise, diet, overweight, and chronic insomnia symptoms.

One commonly cited theory states that the function of sleep is to achieve greater energy conservation beyond the rested wakefulness (Berger & Phillips, 1995). According to this logic, among individuals with chronic insomnia symptoms who may be chronically sleep deprived, both exercise-derived energy expenditure increase and diet-derived energy intake reduction may trigger sleep in order to save energy. Acute or long-term daily exercise was found to improve sleep, particularly in terms of initiating sleep among insomnia patients (Passos et al., 2010; Reid et al., 2010; Passos et al., 2011). A common limitation of previous studies is a lack of energy intake and expenditure measurements, thus it is difficult to infer whether exercise per se or exercise with alteration of energy balance contribute to improved sleep in insomnia. In addition, the association between energy balance and insomnia symptoms may differ between insomniacs with normal weight, overweight/obese, and metabolic syndrome (Vanitallie, 2006). Therefore, further research is warranted to study these groups separately.

A decrease of core body temperature from wake to non-REM (NREM) sleep has long been noticed (Horne & Staff, 1983). Thermoregulation plays an important role between behavioral factors and sleep. Exercise-induced body temperature increases stimulate a down-regulation of core body temperature, and such a 'cool down' process triggers sleep onset (Horne & Staff, 1983). In addition to the down-regulation of core body temperature, thermal dissipation through selective vasodilation of distal skin regions also promotes sleep onset

(Kräuchi et al., 2000). The theory is further strengthened by accumulating evidence which demonstrates the core body thermoregulation function of sleep-related hormones, like serotonin (Murray et al., 2015), gamma-aminobutyric acid (Ishiwata et al., 2005), as well as orexin/hypocretin (Mochizuki et al., 2006; Sun et al., 2013).

There is possibly a vicious circle between disordered sleep and weight gain. Such a bidirectional association is partly attributed to the feeding-related hormones like leptin and ghrelin (Taheri et al., 2004). Leptin is produced by adipose cells as an inhibitor of energy intake. Among overweight or obese individuals, a high leptin level in circulation causes a blunted sensitivity to this hormone, and results in the impairment of the energy intake inhibitory pathway (Brennan & Mantzoros, 2006). At the same time, another hormone named ghrelin, which is secreted by the fasting gastrointestinal tract, increases hunger and thus triggers excessive energy intake (Schwartz et al., 2000). Several cross-sectional studies have investigated whether the levels of leptin and ghrelin differ between group with and without chronic insomnia symptoms, but current results are inconclusive (Motivala et al., 2009; Pan & Kastin, 2014). Similarly to the evidence regarding the link between energy balance and insomnia, further comparative studies should focus on certain groups such as overweight population with chronic insomnia symptoms. Furthermore, orexin/hypocretin, which is directly linked to thermoregulation, feeding, and sleep, needs to be included in such investigations (Riemann & Spiegelhalder, 2014).

## 2.8 Summary of the literature review

In this review, information concerning chronic insomnia symptoms, such as characterization, classification criteria, and prevalence in the population were first introduced. Then there followed an overview of subjective and objective measurements for assessing sleep quality in insomniacs. The main body of the review dealt with the current state of knowledge regarding behavioral risk factors for chronic insomnia symptoms, efficacy of exercise training in treating chronic insomnia symptoms, and effects of diet interventions on sleep quality. On the basis of homeostasis theories, the final part briefly explored mechanisms underlying the relationships between behavioral factors and chronic insomnia symptoms.

# 3 PURPOSE OF THE STUDY

The study is part of a large study that concerns the effects of exercise and diet intervention on quality of sleep among people with obesity-related sleep disorders (Monitoring and treatment of obesity-related sleep disorders, MOTOSD, ISRCTN77172005). This dissertation consists of four publications in scientific journals. The first original article (I) describes the design of the MOTOSD study. The subsequent three articles (II, III, and IV) specifically focused on three main objectives:

1. To investigate whether there are differences in fat mass distribution, lifestyle factors such as physical activity and dietary intakes among middle-aged men with and without chronic insomnia symptoms (II).

2. To test the efficacy of a 6-month aerobic exercise intervention in improving home-based sleep quality among overweight and obese men with chronic insomnia symptoms (III).

3. To test the efficacy of a 6-month diet intervention in improving home-based sleep quality among overweight and obese men with chronic insomnia symptoms (IV).

# 4 MATERIALS AND METHODS

## 4.1 Participants and study design

Participants were Finnish men aged 30 to 65 years. The recruitment of the participants is presented schematically in Figure 2. The detailed descriptions of the participant recruitment are given in the relevant articles (II-IV). The MOTOSD study was approved by the Ethics Committee of the Central Finland Health Care District (Jyväskylä, Finland, 7/2011), and a written informed consent was obtained from all participants prior to the study. Pre-screening and enrolment were carried out by a physician based on sleep questionnaire, health and behavior questionnaire, and participants' medical history. The study was conducted between June 2011 and July 2012.

First a cross-sectional study was performed comparing fat mass distribution (determined by dual-energy x-ray absorptiometry) and behavioral factors between men with and without chronic insomnia symptoms. Participants were 211 men divided into five groups as follows: 1) Normal weight without sleep disorder (HNW); 2) Overweight and obese without sleep disorder (HOW); 3) Overweight and obese with obstructive sleep apnea only (OSA); 4) Overweight and obese with chronic insomnia symptoms only (INS); 5) Overweight and obese with comorbid chronic insomnia symptoms and OSA (COM). OSA among these participants was either classified based on the criteria of a) an Apnea-hypopnea index (AHI, assessed by overnight PSG) of five or greater with excessive daytime sleepiness or an AHI of 15 or greater, regardless of associated symptoms (American Academy of Sleep Medicine Task Force, 1999), or b) based on the criteria for suspected OSA according to the answers in the sleep questionnaire. Classification of insomnia symptoms was based on the DSM-IV-TR criteria (without the criterion of daytime consequences) using the modified version of the Basic Nordic sleep

questionnaire (BNSQ, Partinen & Gislason, 1995). Participants were considered to have chronic insomnia symptoms if they had reported insomnia complaints for over three months, and one or more of the following issues had continuously occurred at least three nights per week for at least one month during the previous three months: 1) Difficulty initiating sleep (DIS, time to fall asleep ≥ 30 minutes); 2) Difficulty maintaining sleep (DMS, awakening during sleep ≥ 3 times/night, or difficulty in falling asleep after nocturnal awakening with total wake after sleep onset ≥ 30 minutes); 3) Early morning awakenings (EMA, wake up ≥ 30 minutes earlier than desired in the morning and unable to fall asleep again); 4) Non-restorative sleep (NRS, not feeling rested or suffering from fatigue upon awakening). In II an additional criterion was applied, namely that insomnia symptoms with the characteristics and frequency as specified above, were present continuously over a period of at least one month during the past three months.

Next a randomized controlled trial was performed that investigated the effects of a 6-month exercise intervention and a 6-month diet intervention on insomnia symptoms. Participants were 73 men (94% overweight or obese, BMI ≥ 25.0) with chronic insomnia symptoms (same insomnia symptom classification criteria with II, however without the requirement of continuous symptom occurrence of one month or longer during the past three months). Men with comorbid insomnia and moderate-severe sleep apnea (AHI ≥ 15) were not involved. Participants were randomized into exercise, diet, or control groups. As the exercise and diet interventions were assumed with independent mechanisms, comparisons of sleep results to the controls for each intervention group were discussed separately in the two manuscripts (III, IV).

Exclusion criteria were: 1) Restless leg syndrome/Periodic leg movement syndrome (periodic leg movement arousal index, PLMs index > 15); 2) Moderate or severe apnea (AHI ≥ 15, only for III and IV); 3) Any medical and surgical care during the past three years related to diseases that might influence sleep quality; 4) Current diagnosis of major depression; 5) History of other major mental illness or substance abuse; 6) History of cognitive impairment and major neurological disorders; 7) History of eating disorders; 8) Present use of very-low-energy diet; 9) Chronic pain conditions; 10) Current or regular use of sedatives, hypnotics (benzodiazepines, benzodiazepine-receptor antagonists, melatonin, etc.), and painkillers; 11) Shift work.

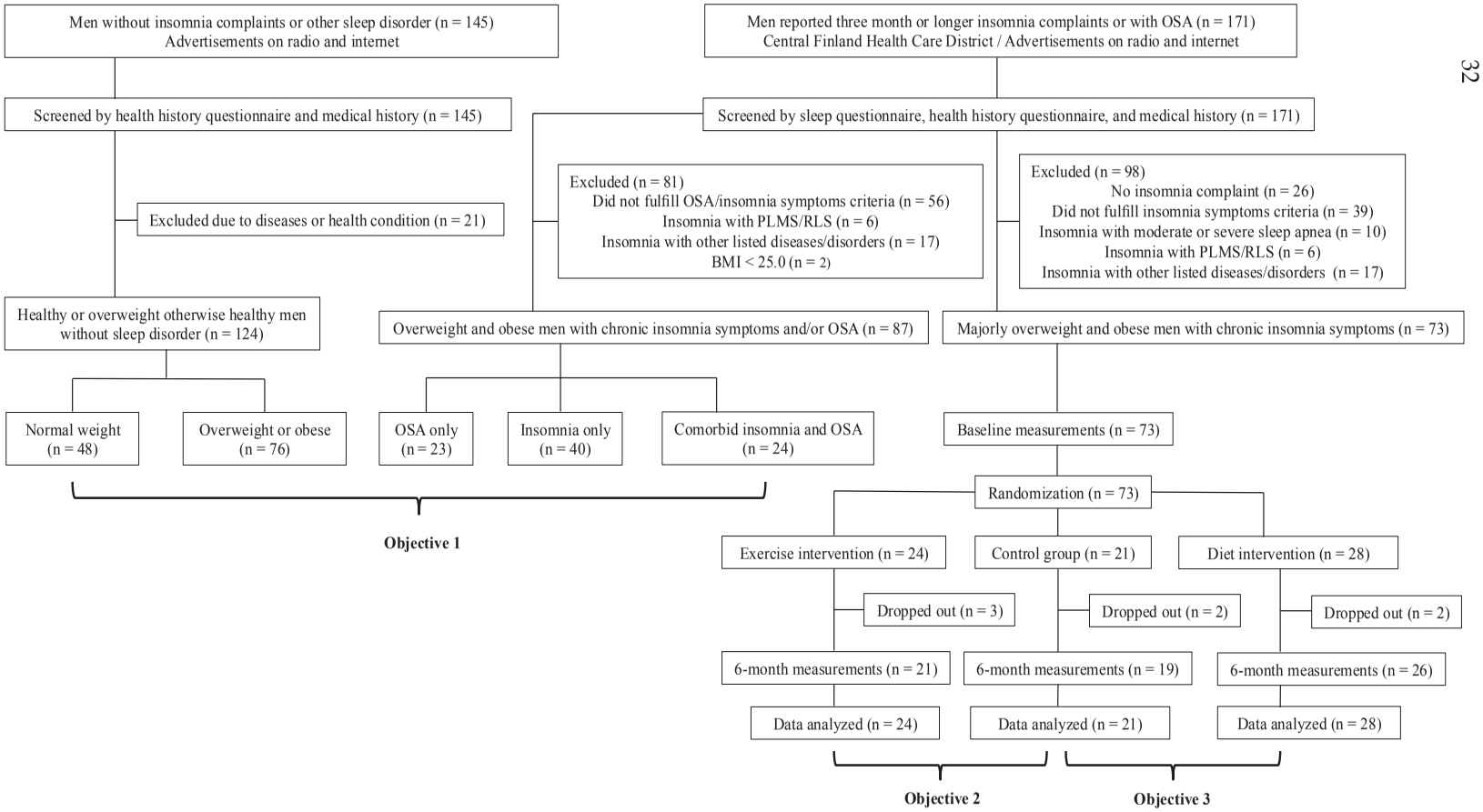



FIGURE 2 Participant flow of the study.

## 4.2 Measurements

All measurements were carried out at baseline before randomization, and at 6 months after the study period (III, IV). In addition, diet diary was completed at 3 months (IV).

### 4.2.1 Background information

Age, education, and smoking habit were collected with the health and behavior questionnaire (II, III, IV). Age of onset of insomnia and occurrence of insomnia symptoms were collected with the sleep questionnaire (III, IV).

### 4.2.2 Anthropometry and fat mass

Height and weight were measured using stadiometer and calibrated physician weight scale, respectively. BMI was calculated as weight (kg) / height$^2$ (m$^2$). Fat mass was determined using dual-energy x-ray absorptiometry (DXA; Prodigy, GE Lunar, Madison, WI, USA).

### 4.2.3 Amount of habitual physical activity

The amount of physical activity was determined as metabolic equivalents (METs) multiplied by duration in minutes (MET mins). The METs of different living activities were taken from the 2011 Compendium of Physical Activities (Ainsworth et al., 2011). For an activity of which intensity level could not be determined due to lack of detailed information, the MET of an average or moderate-intensity level of the activity was substituted. In II, the amount of leisure time physical activity (LTPA) was based on the health and behavior questionnaire. The duration per session, and the number of sessions per week for the two most commonly practiced activities were solicited. Considering the profound climatic differences between seasons in the study region and the possibility that this might affect the choice of exercise activity, the information was solicited separately for the summer (April–September) and winter (October–March) half-years, and the mean values were used in the analyses. In III and IV, the amount of physical activity per day was assessed by 7-day physical activity diary. The diary recorded primary living activity at 30-minute intervals over 24 hours. Physical activities were categorized into exercise and recreational activity, livelihood physical activity, as well as sedentary behaviors and sleep.

### 4.2.4 Dietary intakes

A 3-day diet diary (two weekdays and one weekend day) collected type, item and estimated portion size of all food and drink intake during each day. Input of diet information, calculation of total energy intake and proportions of energy yielding nutrients in total energy intake (E%) were carried out by the Micro-Nutrica software (The Social Insurance Institution of Finland, Turku, Finland).

### 4.2.5 Objective sleep measurement

Home-based objective sleep data were collected by an unobtrusive online sleep monitoring system (Beddit pro; Beddit Ltd., Espoo, Finland) for seven nights. The system included a piezoelectric bed sensor. Ballistocardiographic signals were sampled by the piezoelectric sensor at 140 Hz and simultaneously uploaded to a web server through the Internet, where sleep/wake status was classified in 30-second epochs based on heart rate variability, respiration rate variability, and binary actigram (Paalasmaa et al., 2012). An ambient brightness sensor, included in the system, was placed in the bedroom for determining lights-out time. Measurement was set automatically to start each evening at 18:00, and end at noon the next day. Total sleep time (TST), sleep onset latency (SOL, determined as the duration from being present in bed with lights-out to the first 5 minutes of consecutive sleep) (Morin et al., 2009), wakefulness after sleep onset (WASO), and sleep efficiency (SE) were obtained for each night. Mean values across the measured nights were used for analyses.

### 4.2.6 Subjective sleep measurements

The 7-night sleep diary was collected on the same days as the objective sleep measurement. Items included time of initiating sleep, estimated time of falling asleep, number of nocturnal awakenings, final awakening time, morning-rated subjective quality of sleep, fatigue upon awakening, nap duration, and other issues related with sleep. The mean values of the recorded nights were used for analyses.

Frequency of insomnia symptoms, Epworth Sleepiness Scale (ESS) score, Rimon's depression score, and sleep characteristics were obtained with the sleep questionnaire.

### 4.2.7 Aerobic fitness

The two-kilometer walk test (UKK Institute, Tampere, Finland) was used to determine fitness level. Participants were instructed to walk two kilometers as

fast as possible at a steady pace. Walk time duration and heart rate immediately on finishing the walk were measured for estimation of maximal oxygen uptake (estimated $VO_{2max}$). The fitness index was calculated based on walk time duration, heart rate immediately on finishing the walk, BMI, age and gender (Oja et al., 1991; UKK Institute, 2006). A fitness index less than 70 was defined as low, 70 to 89 as medium, and greater than 89 as high, respectively (UKK Institute, 2006). An exercise watch with a heart rate monitoring belt (M5; Suunto Ltd., Vantaa, Finland) was used to determine heart rate. The test has been proved to be safe for the overweight and obese adults who met our inclusion criteria (Laukkanen et al., 1992).

## 4.3 Randomization

In III and IV, participants were randomized into the exercise intervention, diet intervention, or the control group following baseline measurements by a 1:1:1 ratio (the randomization included moderate to severe apnea patients in the MOTOSD study). Randomization was stratified by age and BMI (≤ or > medians) with a block size of 5, using SAS v. 9.2, (SAS Institute, Cary, NC, USA). A statistician not involved in the study carried out the treatment allocations.

## 4.4 Exercise intervention

A progressive exercise programme was implemented according to fitness levels determined by the baseline fitness test. Nordic walking or other optional aerobic exercise was performed for 30 to 60 minutes per session, one to five sessions per week, for six months (26 weeks), at an intensity level of 60 to 75% of the estimated maximum heart rate obtained by the 2-km walk test. Wrist exercise monitor with heart rate belt (M5; Suunto Ltd., Vantaa, Finland) was used in all exercise sessions for controlling exercise intensity and duration. In addition, each exercise session was finished at least three hours before the bedtime.

## 4.5 Diet intervention

An individualized diet intervention programme was based on the diet diary information and BMI at baseline. Suggested energy-yielding proportions in

total energy consumption were: 40 – 45% of carbohydrate in total energy (E%) with < 5 E% sucrose; 35 – 40 E% fat with 10 E% saturated fat (SFA), 15 – 20 E% monounsaturated fat, and 5 – 10 E% polyunsaturated fat; 20 E% protein. For other nutrients, greater consumptions of dietary fiber, vitamin A, vitamin D, vitamin E, vitamin B, vitamin C, magnesium, and potassium were recommended through suggested food options (The National Nutrition Council of Finland, 2005). Overweight and obese participants were guided to reduce their daily energy intake by 300 – 500 kcal during the first three months, with a target of reducing body weight by 3 kg. After this period, the participants were advised to maintain their achieved body weight reduction, and continue to gradually reduce their body weight towards normal levels. Individualized diet recommendations were introduced to each participant face-to-face by study nutritionists during the first week of intervention. During the 6-month (26 weeks) intervention period, an online diet and nutrition counseling service (MealTracker, MealTracker Ltd., Helsinki, Finland) was utilized 1-3 days per week for assessing each individual's dietary intake and providing personalized feedback. Furthermore, two diet lectures were held during the intervention period.

## 4.6 Control group

Controls were instructed to maintain their habitual lifestyle for six months. They were given an opportunity to participate in the exercise plus diet intervention programme for three months after the study period.

## 4.7 Statistical power

In III and IV, the change of primary outcome of the study: objective SOL was based on published data (Passos et al., 2011). With a balanced allocation of 20 participants per treatment group, estimated statistical power was over 80% to detect a 30% change in SOL in the treatment groups from baseline with no change of SOL in the control group.

## 4.8 Statistical analyses

Statistical analyses were performed by IBM SPSS statistics version 20, or version 22 (SPSS, Inc., Chicago, IL, USA). Analyses related to pre-post intervention

comparisons were carried out following the intention-to-treat principle. For participants with missing or incomplete values at follow-ups, the last observed values were carried forward. All tests were two-tailed, p value less than 0.05 was set as significant. Shapiro-Wilk's W test, and Levene's test were used to examine the normality and homogeneity, respectively. Skewed data were transformed by natural logarithm before further analysis. In II, differences between groups were evaluated by one-way analysis of variance (ANOVA), or the generalized estimating equation, followed with Sidak or *post-hoc* comparisons for multiple comparisons. In III and IV, time by group differences of the outcomes were evaluated by analysis of covariance (ANCOVA) on post-intervention values controlling for the baseline values, followed with Tukey least significant difference *post-hoc* corrections. Within group pre-post intervention differences were evaluated by repeated measures ANOVA. For the diet diary that had an intermediate (3 months) measurement, repeated measures ANOVA were followed with Bonferroni *post-hoc* corrections.

# 5 RESULTS

## 5.1 Characteristics of participants at baseline

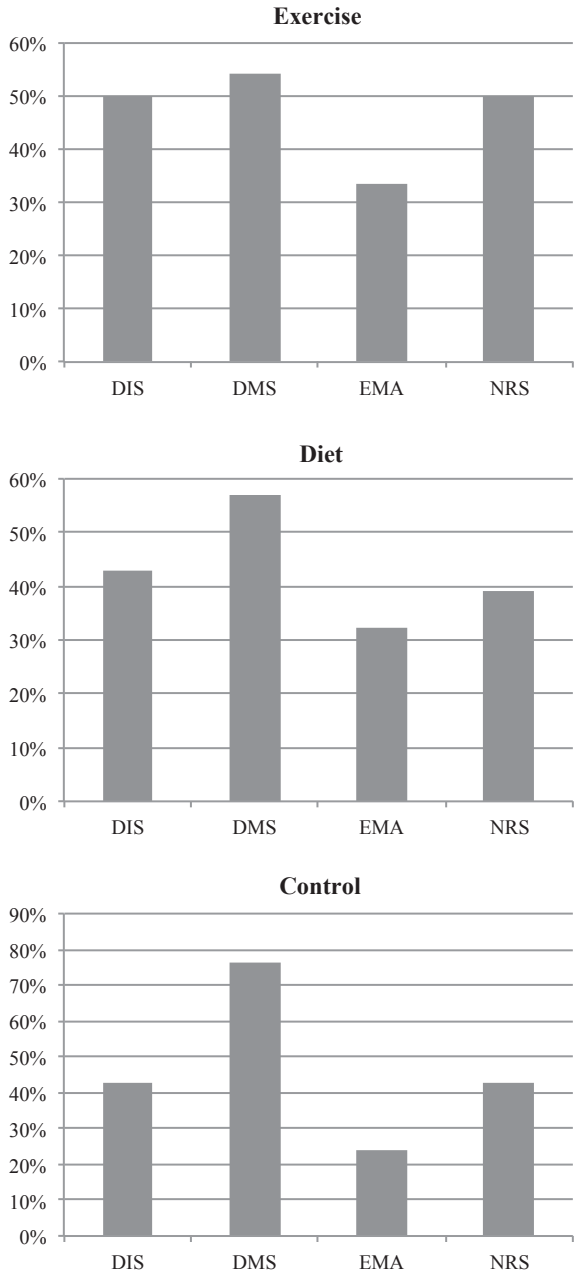
Comparisons of general characteristics at baseline across the five study groups in II and the three randomized groups in III and IV are presented in Table 2. In II, compared to the overweight men without sleep disorders (HOW), body weight and BMI of the participants with OSA only (OSA) or comorbid insomnia symptoms and OSA (COM) were greater ($p \leq 0.001$). Such differences did not exist between the HOW group and overweight men with solely insomnia symptoms (INS). Compared to the normal weight men without sleep disorders (HNW), the proportion of participants who had completed tertiary degree education in the HOW and COM group was lower ($p = 0.012$ and 0.030, respectively), and the proportion of smokers in the HOW and INS group was higher ($p = 0.031$ and 0.015, respectively). General characteristics across the three randomized groups in III and IV did not differ significantly.

The occurrence of chronic insomnia symptoms among the randomized groups in III and IV is presented in Figure 3.

| | II | | | | | III and IV | | |
|---|---|---|---|---|---|---|---|---|
| | **HNW (N=48)** | **HOW (N=76)** | **OSA (N=23)** | **INS (N=40)** | **COM (N=24)** | **Exercise (N=24)** | **Diet (N=28)** | **Control (N=21)** |
| | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| Age (years) | 50.9 (6.8) | 50.4 (7.0) | 52.5 (8.0) | 49.4 (10.0) | 51.3 (9.2) | 51.2 (10.9) | 51.0 (9.7) | 52.6 (10.2) |
| Height (cm) | 178.5 (6.1) | 177.3 (6.0) | 179.8 (7.1) | 179.4 (5.9) | 178.0 (4.5) | 177.4 (6.5) | 178.9 (5.0) | 178.3 (5.8) |
| Weight (kg) | 74.5 (5.7) | 88.5 (9.1) [a] | 100.4 (14.8) [a,b] | 94.0 (11.6) [a] | 99.2 (16.2) [a,b] | 92.3 (14.6) | 93.8 (11.8) | 93.1 (17.2) |
| BMI | 23.4 (1.1) | 28.2 (2.6) [a] | 31.0 (3.9) [a,b] | 29.6 (3.5) [a] | 31.3 (5.0) [a,b] | 29.3 (4.0) | 29.4 (3.7) | 29.2 (4.4) |
| At least tertiary degree education (%) | 97.9 | 86.8 [a] | 91.3 | 95.0 | 80.0 [a] | 91.7 | 82.1 | 95.2 |
| Smoking presently (%) | 6.2 | 18.4 [a] | 17.4 | 25.0 [a] | 24.0 | 29.2 | 14.3 | 19.0 |

Data are presented as Mean (Standard deviation, SD) except for education and smoking habit, for which proportions are given.
HNW, Healthy normal weight; HOW, Overweight or obese otherwise healthy; OSA, Obstructive sleep apnea only; INS, Insomnia symptoms only; COM, Comorbid insomnia symptoms and obstructive sleep apnea.
[a] $p < 0.05$, vs HNW; [b] $p < 0.05$, vs HOW; [c] $p < 0.05$, vs OSA.
p-values refer appropriate test of significance (one-way ANOVA followed with Sidak *post-hoc* comparisons tests for continuous variables and Generalized Estimating Equation for categorical variables).

TABLE 1 General characteristics by study groups at baseline.

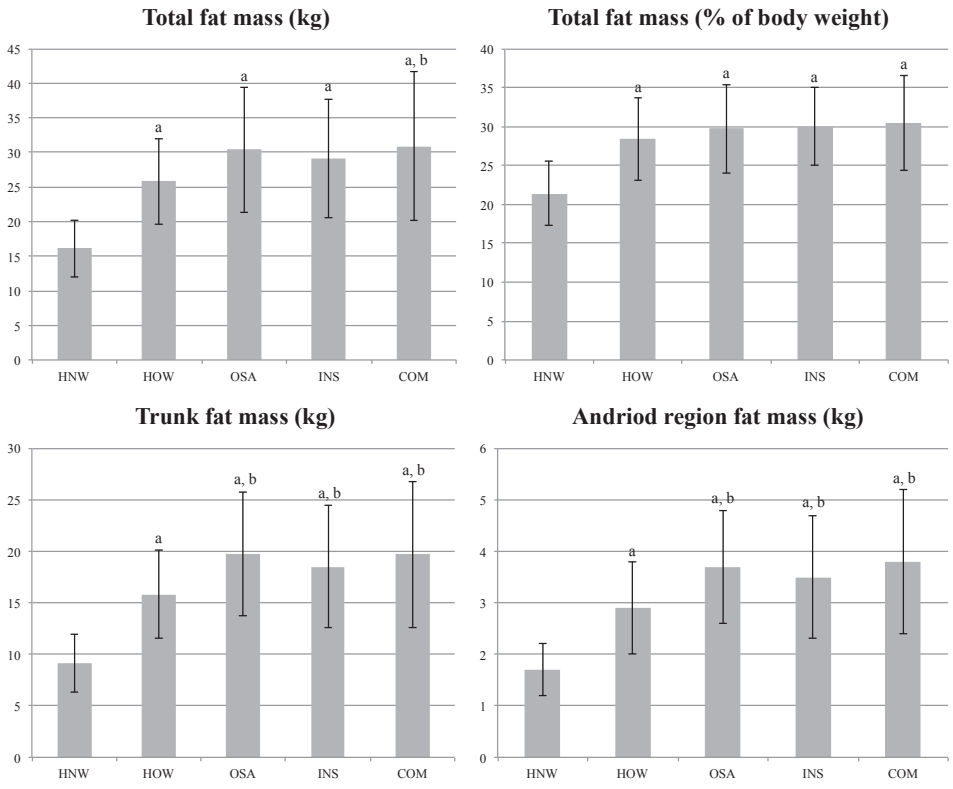



DIS, Difficulty initialting sleep; DMS, Difficulty maintaining sleep;
EMA, Early morning awakeinings; NRS, Non-restorative sleep.

FIGURE 3 Occurrences of chronic insomnia symptoms in the randomized groups.

## 5.2 Fat mass distribution, habitual physical activity, and diet between men with and without chronic insomnia symptoms or OSA (II)

As shown in Figure 4, among the overweight participants, those with comorbid chronic insomnia symptoms and OSA had greater total fat mass than those without sleep disorders (p = 0.039), although the proportion of fat mass in body weight did not differ between the groups. All overweight groups with sleep disorders showed higher fat mass in trunk (p = 0.048 to 0.009) and android regions (p = 0.028 to 0.004) than groups without sleep disorders. Fat mass in other parts of the body (upper and lower limbs, gynoid region) did not differ between the overweight groups (not shown in the figure).




Data are presented as mean ± standard deviation.
HNW, Healthy normal weight; HOW, Overweight or obese otherwise healthy; OSA, Obstructive sleep apnea only; INS, Insomnia symptoms only; COM, Comorbid insomnia symptoms and obstructive sleep apnea.
[a] $p < 0.05$, vs HNW; [b] $p < 0.05$, vs HOW, one-way ANOVA followed with Sidak *post-hoc* corrections.

FIGURE 4 Fat mass distributions in overweight and obese men with and without insomnia symptoms or OSA.

Behavioral factors that differed between overweight men with insomnia symptoms (INS and COM) and their overweight counterparts free from sleep disorders (HOW) are given in Table 3. Compared to the HOW group, INS and COM groups had significantly less leisure time physical activity (LTPA, p = 0.003 and 0.001, respectively), INS showed a lower proportion of energy intake (E%) from carbohydrate, but a higher E% from fat and saturated fatty acids (SFA, p = 0.011 to 0.003), and COM also had higher E% from SFA (p = 0.028). Among the micronutrients, thiamine consumption was lower in both insomniac groups than HOW (p = 0.002 and 0.008, respectively), and folate and potassium consumptions were lower in COM than HOW (p = 0.002 and 0.003, respectively). All the differences remained significant after the adjustment of BMI / BMI, age, education, and smoking habits (p = 0.038 to < 0.001), except for the E% from SFA in the COM vs HOW. In addition, compared to the HOW group, overweight men with OSA but not insomnia symptoms showed no differences for these outcomes (data not presented in the table).

TABLE 2 Differences between overweight men with and without insomnia symptoms, before and after adjustment for covariate(s).

| | Unadjusted | | | Adjusted for BMI | | | Adjusted for BMI, age, education, and smoking habit | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Mean difference** | **p †** | **95% CI** | **Mean difference** | **p ‡** | **95% CI** | **Mean difference** | **p ‡** | **95% CI** |
| **INS vs HOW** | | | | | | | | | |
| LTPA (MET mins/wk) | -549.6 | 0.003 * | (-1010.2, -89.0) | -541.2 | 0.005 * | (-1007.4, -75.0) | -564.5 | 0.005 * | (-1035.5, -93.5) |
| Carbohydrate (E%) | -5.3 | 0.008 | (-9.6, -0.9) | -4.8 | 0.020 | (-9.2, -0.5) | -4.6 | 0.033 | (-9.0, -0.2) |
| Total fat (E%) | 5.0 | 0.003 | (1.2, 8.8) | 4.9 | 0.004 | (1.0, 8.8) | 4.8 | 0.005 | (1.0, 8.6) |
| SFA (E%) | 2.0 | 0.011 | (0.3, 3.8) | 1.9 | 0.032 | (0.1, 3.6) | 1.8 | 0.038 | (0.1, 3.6) |
| Thiamine (mg/1000kcal) | -0.1 | 0.002 | (-0.2, -0.0) | -0.1 | 0.002 | (-0.3, -0.0) | -0.1 | 0.003 | (-0.2, -0.0) |
| **COM vs HOW** | | | | | | | | | |
| LTPA (MET mins/wk) | -642.1 | 0.001 * | (-1201.7, -82.5) | -614.2 | 0.007 * | (-1215.3, -13.0) | -594.6 | 0.009 * | (-1198.6, 9.4) |
| SFA (E%) | 2.3 | 0.028 | (0.1, 4.4) | 1.9 | 0.145 | (-0.3, 4.0) | 2.0 | 0.101 | (-0.2, 4.2) |
| Thiamine (mg/1000kcal) | -0.2 | 0.008 | (-0.3, -0.0) | -0.2 | 0.006 | (-0.3, -0.0) | -0.2 | 0.002 | (-0.3, -0.0) |
| Folate (µg/1000kcal) | -33.1 | 0.002 | (-57.8, -8.5) | -34.3 | 0.002 | (-59.9, -8.6) | -35.8 | 0.001 | (-61.1, -10.5) |
| Potassium (mg/1000kcal) | -415.8 | 0.003 | (-731.5, -100.0) | -459.4 | 0.001 | (-786.8, -132.0) | -478.6 | <0.001 | (-804.5, -152.8) |

COM, Comorbid insomnia and OSA; HOW, Overweight or obese otherwise healthy; LTPA, Leisure-time physical activity; SFA, Saturated fatty acid.

† One-way ANOVA followed with Sidak *post-hoc* comparisons.

‡ Analyses of covariance followed with Sidak *post-hoc* comparisons tests.

* Natural Log-transformed results.

## 5.3 Effects of exercise intervention on sleep among overweight men with chronic insomnia symptoms (III)

Compared to controls, those randomized to the 6-month exercise programme had shorter objective sleep onset latency (SOL, $p = 0.009$) and lower self-reported frequency of difficulty initiating sleep in the preceding three months ($p = 0.028$). Exercisers also showed improvements in objectively measured wake after sleep onset, objective sleep efficiency, subjective nocturnal awakenings, subjective sleep quality, fatigue upon awakening, the Epworth sleepiness scale, and the Rimon's depression score throughout the intervention ($p = 0.047$ to $< 0.001$), but these changes did not have time by group differences (Table 4).

Compared to their own baseline values, habitual amount of exercise and recreational physical activity increased in the exercise group after the intervention ($p = 0.019$), but were unchanged in controls (Figure 5). Total energy expenditure and the amount of other types of physical activity did not change in either group throughout the study. In addition, neither total energy intake nor proportions of energy-yielding nutrient intakes showed a time by group difference (not shown in the figure).

TABLE 3 Sleep, sleepiness, and depression in the randomized groups before and after the study period.

| | Exercise | | Diet | | Control | |
|---|---|---|---|---|---|---|
| | **Baseline** | **6 Months** | **Baseline** | **6 Months** | **Baseline** | **6 Months** |
| **Objective** | | | | | | |
| Total sleep time (min) | 376.8 (353.7 to 399.8) | 390.1 (364.8 to 415.3) | 377.2 (359.0 to 395.4) | 403.3 (384.1 to 422.6) † | 393.3 (370.9 to 415.8) | 412.8 (390.4 to 435.2) |
| Sleep onset latency (min) * | 23.9 (14.0 to 42.2) | 13.7 (6.7 to 22.6) †‡ | 16.6 (11.3 to 27.7) | 9.9 (9.1 to 13.6) †‡ | 18.1 (12.1 to 32.9) | 20.7 (8.8 to 33.4) |
| Wake after sleep onset (min) * | 48.3 (43.9 to 62.2) | 39.1 (35.9 to 52.3) † | 44.7 (36.7 to 53.2) | 42.4 (34.8 to 54.7) | 44.8 (37.2 to 49.4) | 38.7 (34.4 to 49.3) |
| Sleep efficiency (%) * | 81.7 (78.3 to 86.7) | 87.1 (83.1 to 89.3) † | 83.5 (81.5 to 88.2) | 88.1 (85.9 to 90.2) † | 85.9 (82.1 to 88.4) | 86.6 (83.4 to 89.8) |
| **Subjective** | | | | | | |
| Sleep onset latency (min) * | 30.0 (12.0 to 60.0) | 21.0 (12.0 to 40.0) | 21.0 (13.5 to 31.0) | 20.0 (13.3 to 23.8) | 21.5 (17.3 to 41.8) | 25.0 (15.0 to 42.5) |
| Nocturnal awakenings (times/night) | 2.6 (1.8 to 3.3) | 1.9 (1.4 to 2.4) † | 2.3 (1.8 to 2.9) | 1.8 (1.3 to 2.4) † | 2.6 (1.8 to 3.4) | 2.3 (1.8 to 2.8) |
| Morning-rated sleep quality (1-4) [a] | 2.5 (2.3 to 2.7) | 2.7 (2.5 to 2.9) † | 2.4 (2.1 to 2.7) | 2.7 (2.4 to 2.9) | 2.4 (2.2 to 2.5) | 2.4 (2.2 to 2.6) |
| Fatigue upon awakening (1-4) [b] | 2.2 (2.0 to 2.4) | 1.9 (1.7 to 2.1) † | 2.2 (2.0 to 2.4) | 2.0 (1.7 to 2.2) | 1.9 (1.6 to 2.1) | 2.0 (1.8 to 2.2) |
| Difficulty initiating sleep (1-5) [c] | 2.8 (2.2 to 3.3) | 2.2 (1.7 to 2.6) †‡ | 2.5 (2.0 to 3.0) | 2.3 (1.9 to 2.7) | 2.8 (2.2 to 3.3) | 2.7 (2.1 to 3.2) |
| Epworth sleepiness scale score | 8.4 (7.0 to 9.8) | 6.8 (5.5 to 8.1) † | 6.6 (5.2 to 8.0) | 6.3 (4.9 to 7.7) | 8.3 (6.2 to 10.5) | 7.4 (5.2 to 9.7) |
| Rimon's depression score * | 4.0 (2.0 to 7.8) | 2.5 (0.0 to 4.0) † | 5.0 (4.0 to 7.0) | 4.0 (1.3 to 6.0) † | 4.0 (3.0 to 7.5) | 3.0 (2.5 to 5.5) |

Data are shown as Means (95% CI) unless further notified.

* Comparisons under Natural Log transformed data, values are shown as the medians and 25$^{th}$ through 75$^{th}$ percentiles.

† $p < 0.05$, compared to baseline, repeated measures ANOVA.

‡ $p < 0.05$, time-by-group difference compared to control group, analyses of covariance controlling for the baseline values, followed with Tukey least significant difference *post hoc* corrections.

[a] 1 = Very poor; 2 = Relatively poor; 3 = Good; 4 = Excellent.

[b] 1 = Not fatigued at all; 2 = A little fatigued; 3 = Quite fatigued; 4 = Very fatigued.

[c] 1 = Never/less than once per month; 2 = Less than once per week; 3 = 1-2 days per week; 4 = 3-5 days per week; 5 = Daily or almost daily.

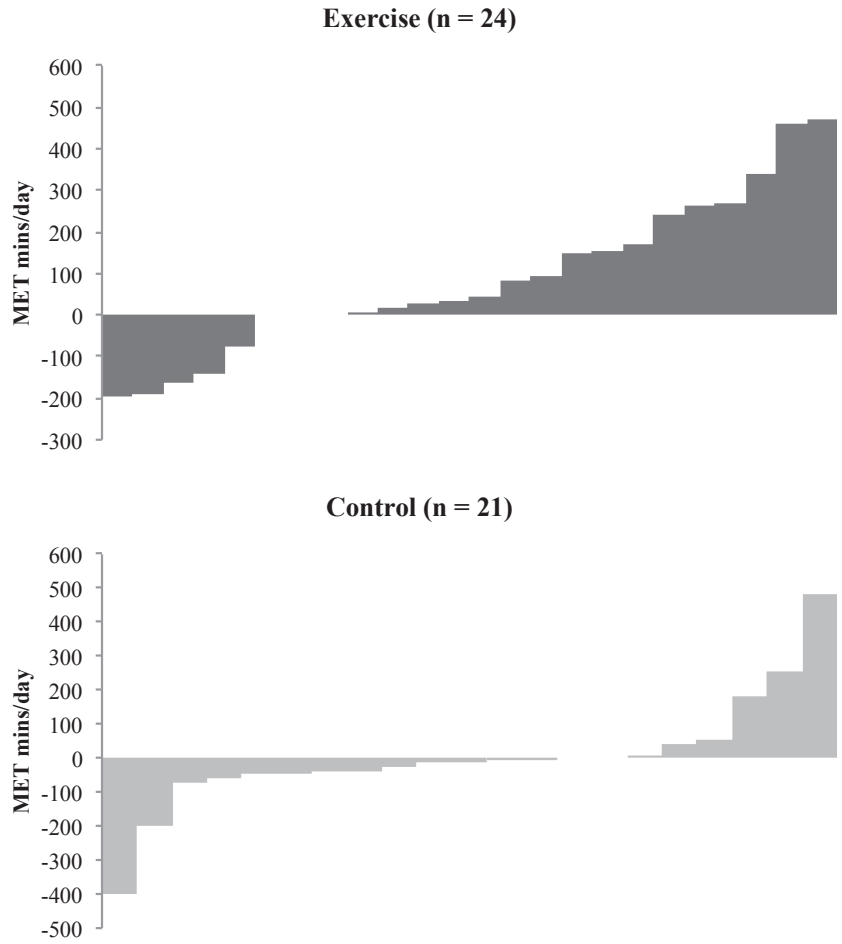


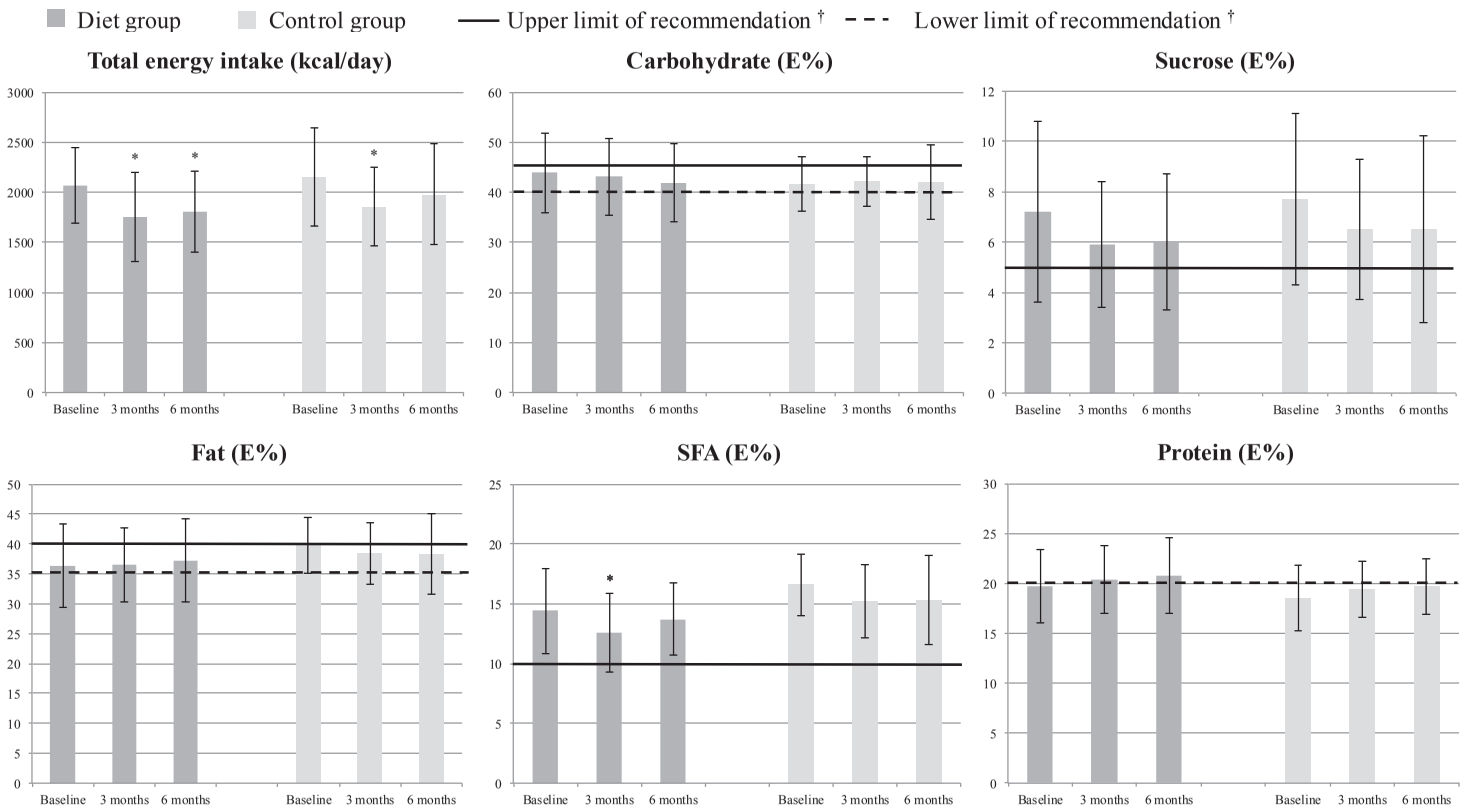

FIGURE 5 Changes of habitual amount of exercise and other recreational physical activity in exercise group and control group.

## 5.4 Effects of diet intervention on sleep among overweight men with chronic insomnia symptoms (IV)

Between the diet and control groups, a time by group difference was seen only in objective sleep onset latency ($p = 0.001$). Within the diet group, improvements following the intervention were exhibited in objective total sleep

time (TST), objective SE, subjective nocturnal awakenings, and the Rimon's depression score ($p = 0.035$ to 0.001, Table 4).

Dietary intakes assessed by 3-day diet diary at the baseline, 3 months, and 6 months are presented in Figure 6. In the diet group, reported total energy intake was significantly reduced during the intervention, and the lowered total energy consumption remained at 6 months. The control group had reduced reported total energy intake at 3 months, but not at 6 months. In both groups, E% from carbohydrates and fats were within the recommended ranges at all measurement timepoints. The diet group also reached the recommended E% from protein through the intervention. In addition, although the E% from SFAs was reduced at 3 months in the diet group, E% from SFAs and sucrose were still higher than the recommended levels.




E%, proportion of total energy intake (alcohol excluded).
Data are presented as means ± standard deviations.
* $p < 0.05$, compared to baseline values, repeated measures ANOVA followed with Bonferroni *post-hoc* corrections.
† Recommendations according to the National Nutrition Council of Finland, 2005.

FIGURE 6 Dietary intakes of diet and control groups at baseline, 3 months, and 6 months.

## 5.5 Changes in body weight, fat mass, and fitness (III and IV)

Body weight, total fat mass, and fitness test results of the three randomized groups throughout the study are presented in Table 5. Compared to controls, the diet group, but not the exercise group had significantly lower body weight ($p = 0.005$) and total fat mass ($p = 0.035$) following the intervention. The difference was due to increased fat mass and total body weight within the control group ($p = 0.027$ and 0.003, respectively). Estimated $VO_{2max}$ and fitness index among both the exercise and the diet group improved relative to baseline ($p = 0.006$ to 0.001).

TABLE 4 Body weight, fat mass, and aerobic fitness level at baseline and 6 months.

| | Exercise | | Diet | | Control | |
|---|---|---|---|---|---|---|
| | **Baseline** | **6 months** | **Baseline** | **6 months** | **Baseline** | **6 months** |
| Body weight (kg) | 92.3 (86.2 to 98.5) | 92.5 (86.6 to 98.4) | 93.8 (89.2 to 98.4) | 92.7 (88.1 to 97.4) ‡ | 93.1 (85.2 to 100.9) | 94.4 (86.3 to 102.5) † |
| Total fat mass (kg) | 27.5 (23.0 to 31.9) | 28.1 (23.3 to 32.9) | 27.5 (24.2 to 30.7) | 26.8 (23.5 to 30.2) ‡ | 28.0 (23.6 to 32.5) | 28.9 (24.0 to 33.8) † |
| Estimated $VO_{2max}$ | 29.3 (25.3 to 33.4) | 31.4 (27.4 to 35.4) † | 27.2 (23.4 to 30.9) | 29.6 (25.4 to 33.9) † | 30.9 (27.1 to 34.8) | 30.4 (26.5 to 34.3) |
| Fitness index | 73.4 (63.2 to 83.6) | 78.6 (68.6 to 88.6) † | 68.2 (58.4 to 78.0) | 74.3 (63.7 to 84.8) † | 78.5 (69.2 to 87.8) | 80.6 (72.0 to 89.3) |

$VO_{2max}$, Maximal oxygen uptake.

Data are shown as Means (95% CI).

† $p < 0.05$, compared to the baseline value, repeated measures analyses of variance.

‡ $p < 0.05$, time-by-group difference compared to control group, analyses of covariance controlling for the baseline values, followed with Tukey least significant difference *post hoc* corrections.

# 6 DISCUSSION

The present study focused on overweight middle-aged men and consisted of two phases. First, body fat distribution and behavioral factors, such as physical activity and diet, were compared between those with and without chronic insomnia symptoms. Second, the efficacy of aerobic exercise training and diet intervention on mitigating chronic insomnia symptoms was investigated.

## 6.1 Fat mass distribution and behavioral factors among overweight men with and without chronic insomnia symptoms

Previous studies have reported associations between reduced sleep time and greater fat mass distributed in the central region of the body (Patel et al., 2008, Chaput et al., 2011), which suggests a potential association between insufficient sleep and central obesity rather than total adiposity. Nevertheless, it is not known whether such an association is related to chronic insomnia symptoms. The fat distribution results in II revealed that even if the total fat mass is comparable, overweight men with chronic insomnia symptoms have greater fat mass concentrated in the trunk and android regions than their counterparts free from sleep disorder. Therefore, central obesity, which is recognized as a risk factor of OSA (Schäfer et al., 2002), is also likely a marker of chronic insomnia symptoms in overweight men.

Sedentary behavior is an independent risk factor of insomnia symptoms among adults (Janson et al., 2001; Haario et al., 2013). In II, we found that regardless of BMI, age, and smoking habits, the amount of leisure time physical activity, but not of other non-occupational physical activities (e.g. housework, commuting), differ between overweight men with and without chronic insomnia symptoms. This result suggests that sedentary behavior or lack of

exercise may be an independent risk factor for chronic insomnia symptoms among overweight and obese men. Similar results have been reported in a previous study of middle-aged women (Kline et al., 2013). In that study, a consistent higher level of exercise activity, but not lifestyle- or household-related activity was associated with better sleep quality.

In II, overweight men with chronic insomnia symptoms had a poorer diet with greater intake of saturated fatty acids and lower consumptions of several micronutrients, compared to those without sleep disorder. It was not until recently that studies started to associate dietary factors with insomnia symptoms (Grandner et al., 2014). The current study results imply that both low physical activity and poor diet may contribute to impaired sleep among the overweight and obese population.

## 6.2 Effect of aerobic exercise training on sleep among overweight men with chronic insomnia symptoms

In III, compared to the control group, exercisers showed reductions in both objective sleep onset latency (SOL) and subjective frequency of difficulty initiating asleep. On the other hand, no time by group difference was found in parameters related to other insomnia symptoms. These results were consistent with those of another study that investigated the effects of exercise on older adults with mild sleep impairment (Chen et al., 2015). Moreover, recent meta-analysis regarding the effects of exercise training on sleep also indicates a stronger effect of exercise on curtailing SOL than other sleep parameters such as total sleep time and sleep efficiency (Kredlow et al., 2015). Thus, it could be that the main influence of regular exercise on insomnia symptoms is in reducing the difficulty of initiating sleep, the symptom which is related to multiple health issues such as heart disease, metabolic syndrome, and mortality (Schwartz et al., 1999; Troxel et al., 2010; Lallukka et al., 2015).

There are several mechanisms for explaining the effects of exercise on sleep onset, such as thermoregulation and energy conservation (Horne & Staff, 1983; Berger & Phillips, 1995). However, in the present study, we were not able to find clear evidence that would support the above-mentioned mechanisms. An exercise-induced core body temperature increase could trigger a significant decrease in sleep onset time (Horne & Staff, 1983), but this is for the acute effect, which was not measured in our study. Furthermore, under the logic of energy conservation theory, we assumed that the chronic effect of energy balance alteration was a key mechanism behind the effect of exercise on sleep initiating among overweight and obese men. Nevertheless, no time-by-group or within group pre-post intervention differences were found in total energy intake or

expenditure (assessed by 3-day diet diary and 7-day physical activity diary, respectively). Future studies with pre-post intervention as well as intermediate measurements of energy intake, energy expenditure, and sleep parameters are needed to verify whether long-term energy balance alteration is the main reason for shortening SOL.

## 6.3 Effects of energy intake reduction and nutrient composition adjustment on sleep among overweight men with chronic insomnia symptoms

A recent study reported that compared to a 2-day ad-libitum diet, polysomonography determined sleep quality was better following a 4-day energy-controlled diet among normal sleepers (St-Onge et al., 2016). Specifically, SOL was longer, and slow wave sleep duration was shorter after the ad-libitum feeding. This study, together with others (Wells et al., 1997, Perron et al., 2015), indicates the acute effects of diet alteration on sleep. In IV, we aimed to investigate whether long-term diet alteration by both reducing energy intake and adjusting macronutrient composition could improve sleep quality among insomniacs. Similar to the effects of regular exercise, objective SOL was curtailed following the diet intervention compared to the controls. Therefore, among overweight and obese men, sleep initiation may be improved by the lowered total energy consumption and/or a more balanced diet composition.

Finally, it is worth mentioning that, compared to the controls, diet intervention led to lower body weight and total fat mass, but no such difference was observed between the exercise and control groups. The controls increased their weight and fat mass during the study period, while the exercise group had no changes, and the diet group showed a slight trend for these parameters to decrease. These results suggest two points. First, in addition to short sleep duration (Shechter et al., 2012), chronic insomnia symptoms also contribute to weight gain. Second, the altered energy-balance is likely to play a role in diet induced sleep alteration. Nevertheless, further studies are needed for elucidating the underlying mechanisms.

## 6.4 Strengths and limitations

The present study is among the first to investigate the effects of behavioral factors on sleep among an overweight population with chronic insomnia symptoms in a randomized setting. Compared to other relevant studies, this study had several strengths. First, in addition to the simple anthropometry

measurements, dual energy x-ray densitometry was used to assess body composition. Second, the randomized controlled trial (III and IV) enabled us to obtain more robust results than many previous studies which have lacked control groups. Furthermore, both objective and subjective sleep assessments were performed at home on multiple nights, which minimized the effects of sleep environment switching (to sleep lab), and night-to-night sleep variability.

This study was subject to some limitations. First, the study involved only male participants, and thus restricted us from knowing if the same cross-sectional differences and interventional effects also exist among women. Second, the INS group in II and participants in III and IV might also be affected by sleep apnea, due to the underestimation of suspected apnea criteria in the sleep questionnaire, and this might lead to heterogeneity in the insomniac population.

In II, participants without sleep disorder were overweight or obese men who were otherwise healthy, therefore the differences observed in fat mass distribution and behavioral factors may not exist in overweight/obese populations with other comorbid pathologies.

In III and IV, objective sleep measurement was carried out by a piezoelectric system with a new algorithm. Although the initial validation against PSG showed satisfactory accuracy in determining sleep/wake status, further validations against both PSG and wrist actigraphy are needed. Furthermore, due to the nature of lifestyle intervention, we were not able to blind the participants in the control group, and hence the Hawthorne effect might have altered their behavior in terms of physical activity and diet. Finally, the underlying mechanisms of the effects of exercise and diet on sleep were not investigated in this study, which should be focused in the future.

# 7 MAIN FINDINGS AND CONCLUSIONS

1. Compared to overweight and obese men free from sleep disorders and other major pathologies, overweight and obese middle-aged men with chronic insomnia symptoms had more adipose tissue in the central body region, less leisure time physical activity, and poorer diet.

2. Six-month aerobic training improved both objective and subjective sleep quality among (mostly) overweight men with chronic insomnia symptoms, regardless of change in body weight or fat mass. The improvement is mainly demonstrated as eased difficulty in initiating sleep.

3. Six-month diet intervention by reducing energy intake and optimizing diet composition improved sleep quality among overweight men with chronic insomnia symptoms, particularly by curtailing objective sleep onset latency. The improvement in sleep may partly be attributed to decreased body weight and fat mass.

# YHTEENVETO (FINNISH SUMMARY)

Ihmiset käyttävät arviolta noin kolmanneksen elinajastaan nukkumiseen. Univaikeuksista johtuva riittämätön uni ja huono unen laatu ovat monien sairauksien, esimerkiksi muistisairauksien, sydän- ja verisuonisairauksien ja tyypin 2 diabeteksen riskitekijöitä. Krooninen unettomuus on yleisin unihäiriö, ja se on hyvin yleistä aikuisilla niin Suomessa kuin muissakin kehittyneissä maissa. Nykyisissä kroonisen unettomuuden hoitomenetelmissä on kuitenkin puutteita, kuten lääkehoitojen haittavaikutukset ja käyttäytymisterapioiden saatavuuden ongelmat ja korkeahkot kustannukset. Siksi unettomuusoireita helpottamaan tarvitaan vaihtoehtoisia menetelmiä.

On lisääntyviä todisteita siitä, että elintapatekijät kuten liikunnan puute ja epätasapainoinen ruokavalio, jotka liittyvät lievään (painoindeksin mukaan määritelty BMI ≥ 25.0 ja ≤ 29.9) tai merkittävään (BMI ≥ 30.0) ylipainoon, ovat yhteydessä uneen ja unettomuusoireisiin. Siksi sellaisten ihmisten määrä, joilla on samanaikaisia ylipaino- ja unettomuusoireita, on todennäköisesti valtava. Siitä huolimatta on vain muutamia tutkimuksia, joissa on tutkittu unettomuusoireita vain ylipainoisilla ihmisillä, ja siksi mahdollisten elämäntapatekijöiden yhteys unettomuusoireisiin on epäselvä.

Interventiotutkimukset osoittavat fyysisen harjoituksen ja dieetin vaikutukset uneen. Aerobisen harjoituksen on raportoitu olevan tehokas tapa parantaa unen laatua kroonisesta unettomuudesta kärsivillä potilailla. Tämä tutkimus osoittaa myös jyrkän dieettimuutoksen suorat vaikutukset uniparametreihin. Täten molemmilla menetelmillä on mahdollista helpottaa unettomuusoireita. Toistaiseksi kuitenkin satunnaisotantaan perustuvat kontrolloidut yritykset tutkia sekä harjoituksen että ruokavalion vaikutuksia unettomuuteen ovat harvinaisia.

Tässä poikkileikkaustutkimuksessa selvitettiin käyttäytymistekijöitä, jotka liittyivät kroonisiin unettomuusoireisiin ylipainoisilla miehillä. Sen lisäksi aerobisten harjoitusten ja dieettimuutosten vaikutuksia tässä joukossa tutkittiin satunnaistetulla kontrollikokeella. Poikkileikkaustutkimukseen osallistui 211 keski-ikäistä suomalaismiestä joilla oli tai ei ollut unettomuusoireita. Painoindeksi mitattiin DXA-menetelmällä (dual-energy x-ray absorptiometry; Prodigy, GE Lunar, Madison, Wi, USA) ja tavanomaisen fyysisen liikunnan määrä ja dieetin koostumus arvioitiin kyselylomakkeilla ja kolmen päivän dieettipäiväkirjan avulla. Tutkimuksessa verrattiin ylipainoisia osanottajia, joilla oli tai ei ollut unettomuusoireita. Tilastollisten erojen laskemisessa käytettiin yksisuuntaista varianssi-analyysia hyödyntäen Sidak *post-hoc* korjauksia. Verrattuna ylipainoisiin verrokkeihin, joilla ei ollut univaikeuksia, ylipainoisilla kroonisista unettomuusoireista kärsivillä miehillä oli korkeampi

keskivartalon alueen painoindeksi (vartalo ja vatsanseutu, p = 0.048 - 0.004), vähemmän vapaa-ajan fyysisiä aktiviteetteja (p = 0.003 - 0.001) ja he käyttivät enemmän tyydyttyneitä rasvoja kokonaisenergian hankinnassa (p = 0.028 - 0.003). Nämä erot olivat pysyviä vielä BMI:tä, ikää, koulutustaustaa ja tupakointia koskevien korjausten jälkeen (p = 0.038 - 0.005).

Satunnaistetussa kontrollikokeessa 73 keski-ikäistä suomalaista miestä (94% ylipainoisia), joilla oli kroonisia unettomuusoireita, osallistui satunnaistetusti liikuntaryhmään, dieettiryhmään tai kontrolliryhmään. Liikuntaryhmä osallistui kuuden kuukauden pituiseen interventiojaksoon, joka koostui 1-5 liikuntakerrasta viikossa, joista kukin kesti 30 - 60 minuuttiin. Harjoituksen määrä ja kertojen tiheys yksilöllistettiin osallistujan kunnon mukaan. Dieettiryhmä oli mukana kuuden kuukauden yksilöllisessä dieettiohjelmassa, jossa neuvonta tapahtui sekä kasvokkain että netin välityksellä (Mealtracker.fi, Wellness Foundry Holding Oy, Helsinki, Suomi). Dieettitavoitteena oli 300 – 500 kcal vähentäminen päivittäisestä energiansaannista ja optimaaliset suhteet dieetin koostumuksessa energiaa tuottavaa ravintoa vähentämällä ja hivenaineita lisäämällä. Kontrolliryhmää neuvottiin jatkamaan aiempaa elintapaansa. Uniparametrit mitattiin kotona seitsemänä yönä käyttäen sensoria (Piezoelectric bed sensor, Beddit Pro, Beddit Oy, Espoo, Suomi) ja unipäiväkirjaa. Muita menetelmiä olivat Pohjoismaisen unikyselyn (Basic Nordic Sleep Questionnaire, BNSQ) mukailtu versio, antropometriset mittaukset, painoindeksi (DXA), kolmen päivän dieettipäiväkirja, päiväkirja seitsemän päivän fyysisistä aktiviteeteista ja kuntotesti (2 km kävelytesti). Tilastolliset analyysit tehtiin käyttämällä kovarianssianalyysia. Kontrolliryhmään verrattuna liikunta- tai dieetti-interventio ryhmään kuuluvilla oli lyhyempi nukahtamisaika kuuden kuukauden kuluttua (p = 0.009 ja 0.001, vastaavasti), ja fyysisesti harjoitelleiden ryhmässä myös heidän itsensä raportoima nukahtamisvaikeuksien määrä laski (p = 0.028).

Tämä tutkimus on ensimmäisiä tutkimuksia, joissa on tutkittu käyttäytymistekijöiden vaikutusta ylipainoisilla, joilla on kroonisia unettomuusoireita. Tutkimus valaisee ylipainoisuuteen liittyvien elintapatekijöiden ja kroonisten unettomuusoireiden yhteyksiä. Aerobisen liikunnan lisäämisellä ja ruokavaliolla voidaan parantaa unta ja erityisesti nukahtamista. Liikuntaharjoituksien lisäämistä ja dieetti-interventioita tulisikin harkita aina hoidettaessa unettomuutta ylipainoisilla.

Ydinsanat: unettomuus, unettomuusoireet, ylipaino, liikunta, dieetti, ravitsemus, nukahtamisaika, miehet

## REFERENCES

American Academy of Sleep Medicine 2014. International Classification of Sleep Disorders.3rd ed. Darien, IL: American Academy of Sleep Medicine.

American Academy of Sleep Medicine 2005. The International Classification of Sleep Disorders: diagnostic and coding manual. (2nd ed.). Westchester, IL: American Academy of Sleep Medicine.

American Academy of Sleep Medicine Task Force 1999. Sleep-relatedbreathing disorders in adults: recommendations for syndromedefinition and measurement techniques in clinical research. Sleep 22, 667–689.

Ainsworth, B.E., Haskell, W.L., Herrmann, S.D., Meckes, N., Bassett, D.R. Jr., Tudor-Locke, C., Greer, J.L., Vezina, J., Whitt-Glover, M.C. & Leon, A.S. 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. Medicine & Science in Sports & Exercise 43, 1575-1581.

Altman, N.G., Izci-Balserak, B., Schopfer, E., Jackson, N., Rattanaumpawan, P., Gehrman, P.R., Patel, N.P. & Grandner, M.A. 2012. Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. Sleep Medicine 13(10), 1261-1270.

American Psychiatric Association 2000. Diagnostic and Statistical Manual Of Mental Disorders, 4th edn, text revision. Washington DC: American Psychiatric Assiciation.

American Psychiatric Association 2013. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association.

Baron, K.G., Reid, K.J. & Zee, P.C. 2013. Exercise to improve sleep in insomnia: exploration of the bidirectional effects. Journal of Clinical Sleep Medicine 9(8), 819-824.

Benedict, C., Byberg, L., Cedernaes, J., Hogenkamp, P.S., Giedratis, V., Kilander, L., Lind, L., Lannfelt, L. & Schiöth, H.B. 2015. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. Alzheimer's & Dementia 11(9), 1090-1097.

Berger, R.J. & Phillips, N.H. 1995. Energy conservation and sleep. Behavioral Brain Research 69(1-2), 65-73.

Blackwell, T., Redline, S., Ancoli-Israel, S., Schneider, J.L., Surovec, S., Johnson, N.L., Cauley, J.A., Stone, K.L. & Study of Osteoporotic Fractures Research Group. 2008. Comparison of sleep parameters from actigraphy and polysomnography in older women: the SOF study. Sleep 31(2), 283-291.

Brennan, A.M. & Mantzoros, C.S. 2006. Drug Insight: the role of leptin in human physiology and pathophysiology--emerging clinical applications. Nature Clinical Practice. Endocrinology & Metabolism 2(6), 318-327.

Brower, K.J. 2015. Assessment and treatment of insomnia in adult patients with alcohol use disorders. Alcohol 49(4), 417-427.

Buysse, D.J. 2008. Chronic insomnia. American Journal of Psychiatry 165(6), 678-686.

Buysse, D.J. 2013. Insomnia. The Journal of American Medical Association 309(7), 706-716.

Buysse, D.J., Reynolds, C.F. 3rd., Monk, T.H., Berman, S.R. & Kupfer, D.J. 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research 28(2), 193-213.

Cappuccio, F.P., Cooper, D., D'Elia, L., Strazzullo, P. & Miller, M.A. 2011. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. European Heart Journal 32(12), 1484-1492.

Cappuccio, F.P., Taggart, F.M., Kandala, N.B., Currie, A., Peile, E., Stranges, S. & Miller, M.A. 2008. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31(5), 619-626.

Carney, C.E., Buysse, D.J., Ancoli-Israel, S., Edinger, J.D., Krystal, A.D., Lichstein, K.L. & Morin, C.M. 2012. The consensus sleep diary: standardizing prospective sleep self-monitoring. Sleep 35(2), 287-302.

Chaput, J.P., Després, J.P., Bouchard, C. & Tremblay, A. 2011. Short sleep duration preferentially increases abdominal adiposity in adults: preliminary evidence. Clinical Obesity 1, 141–146.

Chen, L.J., Fox, K.R., Ku, P.W. & Chang, Y.W. 2015. Effects of aquatic exercise on sleep in older adults with mild sleep impairment: a randomized controlled trial. International Journal of Behavioral Medicine, May 30.

Chung, K.F., Yeung, W.F., Ho, F.Y., Yung, K.P., Yu, Y.M. & Kwok, C.W. 2015. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). Sleep Medicine 16, 477-482.

Clark, I. & Landolt, H.P. 2016. Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. Sleep Medicine Reviews, Jan 30. pii: S1087-0792(16)00015-0. doi: 10.1016/j.smrv.2016.01.006.

Colten, H.R. & Altevogt, B.M. 2006. Institute of Medicine Committee on sleep medicine and research. Sleep disorders and sleep deprivation: an unmet public health problemInstitute of Medicine, Washington, DC: National Academies Press.

Crönlein, T., Langguth, B., Busch, V., Rupprecht, R. & Wetter, T.C. 2015. Severe chronic insomnia is not associated with higher body mass index. Journal of Sleep Research 24(5), 514-517.

Daley, M., Morin, C.M., LeBlanc, M., Grégoire, J.P. & Savard, J. 2009. The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers. Sleep 32(1), 55-64.

Dzierzewski, J.M., Buman, M.P., Giacobbi, P.R. Jr., Roberts, B.L., Aiken-Morgan, A.T., Marsiske, M. & McCrae, C.S. 2014. Exercise and sleep in community-dwelling older adults: evidence for a reciprocal relationship. Journal of Sleep Research 23(1), 61-68.

Edinger, J.D., Marsh, G.R., McCall, W.V., Erwin, C.W. & Lininger, A.W. 1991. Sleep variability across consecutive nights of home monitoring in older mixed DIMS patients. Sleep 14(1), 13-17.

Edinger, J.D., Wohlgemuth, W.K., Radtke, R.A., Marsh, G.R. & Quillian, R.E. 2001. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. The Journal of American Medical Association, 285(14), 1856-1864.

Espie, C.A., Kyle, S.D., Williams, C., Ong, J.C., Douglas, N.J., Hames, P. & Brown, J.S. 2012. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. Sleep 35(6), 769-781.

Fabsitz, R. R., Sholinsky, P. & Goldberg, J. 1997. Correlates of insomnia symptoms among men: the Vietnam Era Twin Registry. Journal of Sleep Research 6, 50–56.

Farina, B., Dittoni, S., Colicchio, S., Testani, E., Losurdo, A., Gnoni, V., Di Blasi, C., Brunetti, R., Contardi, A., Mazza, S., Della Marca, G. 2014. Heart rate and heart rate variability modification in chronic insomnia patients. Behavioral Sleep Medicine 12(4), 290-306.

Fogelholm, M., Kronholm, E., Kukkonen-Harjula, K., Partonen, T., Partinen, M. & Härmä, M. 2007. Sleep-related disturbances and physical inactivity are independently associated with obesity in adults. International Journal of Obesity (Lond) 31(11), 1713-1721.

Ford, E.S., Wheaton, A.G., Cunningham, T.J., Giles, W.H., Chapman, D.P. & Croft, J.B. 2014. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care survey 1999-2010. Sleep 37(8), 1283-1293.

Gao, X., Schwarzschild, M.A., Wang, H. & Ascherio, A. 2009. Obesity and restless legs syndrome in men and women. Neurology 72(14), 1255-1261.

Grandner, M.A., Jackson, N., Gerstner, J.R. & Knutson, K.L. 2014. Sleep symptoms associated with intake of specific dietary nutrients. Journal of Sleep Research 23, 22-34.

Greenblatt, D.J. & Roth, T. 2012. Zolpidem for insomnia. Expert Opinion on Pharmacotherapy 13(6), 879-893.

Guilleminault, C., Clerk, A., Black, J., Labanowski, M., Pelayo, R. & Claman, D. 1995. Nondrug treatment trials in psychophysiologic insomnia. Archives of Internal Medicine 155(8), 838-844.

Haario, P., Rahkonen, O., Laaksonen, M., Lahelma, E. & Lallukka, T. 2013. Bidirectional associations between insomnia symptoms and unhealthy behaviours. Journal of Sleep Research 22: 89-95.

Härmä, M., Tenkanen, L., Sjöblom, T., Alikoski, T. & Heinsalmi, P. 1998. Combined effects of shift work and life-style on the prevalence of insomnia, sleep deprivation and daytime sleepiness. Scandinavian Journal of Work, Environment & Health 24(4), 300-307.

Hartescu, I., Morgan, K. & Stevinson, C.D. 2015. Increased physical activity improves sleep and mood outcomes in inactive people with insomnia: a randomized controlled trial. Journal of Sleep Research 24(5), 526-534.

Hauri, P.J. & Wisbey, J. 1992. Wrist actigraphy in insomnia. Sleep 15(4), 293-301.

Heatley, E.M., Harris, M., Battersby, M., McEvoy, R.D., Chai-Coetzer, C.L. & Antic, N.A. 2013. Obstructive sleep apnoea in adults: a common chronic condition in need of a comprehensive chronic condition management approach. Sleep Medicine Reviews 17(5), 349-355.

Horne, J.A. & Staff, L.H. 1983. Exercise and sleep: body-heating effects. Sleep 6(1), 36-46.

Ishiwata, T., Saito, T., Hasegawa, H., Yazawa, T., Kotani, Y., Otokawa, M. & Aihara, Y. 2005. Changes of body temperature and thermoregulatory responses of freely moving rats during GABAergic pharmacological stimulation to the preoptic area and anterior hypothalamus in several ambient temperatures. Brain Research 1048(1-2), 32-40.

Jaehne, A., Unbehaun, T., Feige, B., Lutz, U.C., Batra, A. & Riemann, D. 2012. How smoking affects sleep: a polysomnographical analysis. Sleep Medicine 13(10), 1286-1292.

James, P.T. 2004. Obesity: the worldwide epidemic. Clinics in Dermatology 22(4), 276-280.

Janson, C., Lindberg, E., Gislason, T., Elmasry, A. & Boman, G. 2001. Insomnia in men - a 10-year prospective population based study. Sleep 24, 425-430.

Kahlhöfer, J., Karschin, J., Breusing, N. & Bosy-Westphal, A. 2016. Relationship between actigraphy-assessed sleep quality and fat mass in college students. Obesity (Silver Spring) 24(2), 335-341.

King, A.C., Oman, R.F., Brassington, G.S., Bliwise, D.L. & Haskell, W.L. 1997. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. The Journal of American Medical Association 277(1), 32-37.

King, A.C., Pruitt, L.A., Woo, S., et al. 2008. Effects of moderate-intensity exercise on polysomnographic and subjective sleep quality in older adults

with mild to moderate sleep complaints. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 63, 997-1004.

Kitano, N., Tsunoda, K., Tsuji, T., Osuka, Y., Jindo, T., Tanaka, K. & Okura, T. 2014. Association between difficulty initiating sleep in older adults and the combination of leisure-time physical activity and consumption of milk and milk products: a cross-sectional study. BMC Geriatrics 14, 118.

Kline, C.E. 2014. The bidirectional relationship between exercise and sleep: Implications for exercise adherence and sleep improvement. American Journal of Lifestyle Medicine 8(6), 375-379.

Kline, C.E., Irish, L.A., Krafty, R.T., et al. 2013. Consistently high sports/exercise activity is associated with better sleep quality, continuity and depth in midlife women: the SWAN sleep study. Sleep 36, 1279-1288.

Kline, C.E., Lubinski, L.C., Seres, R.J., Miewald, J.M., Hall, M.H. & Buysse, D.J. 2014. Improved sleep quality does not result in increased daytime activity in older adults with insomnia. Medicine & Science in Sports & Exercise 46, S434.

Kräuchi, K., Cajochen, C., Werth, E. & Wirz-Justice, A. 2000. Functional link between distal vasodilation and sleep-onset latency? The American Journal of Physiology - Regulatory, Integrative and Comparative Physiology 278(3), R741-748.

Kredlow, M.A., Capozzoli, M.C., Hearon, B.A., Calkins, A.W. & Otto, M.W. 2015. The effects of physical activity on sleep: a meta-analytic review. Journal of Behavioral Medicine 38(3), 427-449.

Kurotani, K., Kochi, T., Nanri, A., et al. 2015. Dietary patterns and sleep symptoms in Japanese workers: the Furukawa Nutrition and Health Study. Sleep Medicine 16, 298-304.

Lallukka, T., Arber, S., Rahkonen, O. & Lahelma, E. 2010. Complaints of insomnia among midlife employed people: the contribution of childhood and present socioeconomic circumstances. Sleep Medicine 11, 828-836.

Lallukka, T., Kaikkonen, R., Härkänen, T., Kronholm, E., Partonen, T., Rahkonen, O. & Koskinen, S. 2014. Sleep and sickness absence: a nationally representative register-based follow-up study. Sleep 37(9), 1413-1425.

Lallukka, T., Podlipskytė, A., Sivertsen, B., Andruškienė, J., Varoneckas, G., Lahelma, E., Ursin, R., Tell, G.S. & Rahkonen, O. 2015. Insomnia symptoms and mortality: a register-linked study among women and men from Finland, Norway and Lithuania. Journal of Sleep Research, Sep 30.

Lambiase, M.J., Gabriel, K.P., Kuller, L.H. & Matthews, K.A. 2013. Temporal relationships between physical activity and sleep in older women. Medicine & Science in Sports & Exercise 45(12), 2362-2368.

Laukkanen, R., Oja, P., Pasanen, M. & Vuori, I. 1992. Validity of a two kilometre walking test for estimating maximal aerobic power in overweight adults.

International Journal of Obesity and Related Metabolic Disorders 16, 263-268.

Lichstein, K.L., Stone, K.C., Donaldson, J., Nau, S.D., Soeffing, J.P., Murray, D., Lester, K.W. & Aguillard, R.N. 2006. Actigraphy validation with insomnia. Sleep 29(2), 232-239.

Mang, G.M., Nicod, J., Emmenegger, Y., Donohue, K.D., O'Hara, B.F. & Franken, P. 2014. Evaluation of a piezoelectric system as an alternative to electroencephalogram/ electromyogram recordings in mouse sleep studies. Sleep 37(8), 1383-1392.

Marino, M., Li, Y., Rueschman, M.N., Winkelman, J.W., Ellenbogen, J.M., Solet, J.M., Dulin, H., Berkman, L.F. & Buxton, O.M. 2013. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep 36(11), 1747-1755.

Massa, J., Stone, K.L., Wei, E.K., Harrison, S.L., Barrett-Connor, E., Lane, N.E., Paudel, M., Redline, S., Ancoli-Israel, S., Orwoll, E. & Schernhammer, E. 2015. Vitamin D and actigraphic sleep outcomes in older community-dwelling men: the MrOS sleep study. Sleep 38(2), 251-257.

Meisinger, C., Heier, M., Loewel, H., MONICA/KORA Augsburg Cohort Study. 2005. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. Diabetologia 48(2), 235-241.

Morin, A.K., Jarvis, C.I. & Lynch, A.M. 2007. Therapeutic options for sleep-maintenance and sleep-onset insomnia. Pharmacotherapy 27(1), 89–110.

Morin, C.M. 1993. Insomnia: psychological assessment and management. New York: Guilford Press.

Morin, C.M., Vallières, A., Guay, B., Ivers, H., Savard, J., Mérette, C., Bastien, C. & Baillargeon, L. 2009. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. The Journal of American Medical Association 301(19), 2005-2015.

Morgan, K. 2003. Daytime activity and risk factors for late-life insomnia. Journal of Sleep Research 12(3), 231-238.

Motivala, S.J., Tomiyama, A.J., Ziegler, M., Khandrika, S. & Irwin, M.R. 2009. Nocturnal levels of ghrelin and leptin and sleep in chronic insomnia. Psychoneuroendocrinology 34(4), 540-545.

Mozaffarian, D., Hao, T., Rimm, E.B., Willett, W.C. & Hu, F.B. 2011. Changes in diet and lifestyle and long-term weight gain in women and men. New England Journal of Medicine 364(25), 2392-2404.

Murray, N.M., Buchanan, G.F. & Richerson, G.B. 2015. Insomnia Caused by Serotonin Depletion is Due to Hypothermia. Sleep 38(12), 1985-1993.

Ohayon, M.M. 2002. Epidemiology of insomnia: What we know and what we still need to learn. Sleep Medicine Reviews 6(2), 97–111.

Ohayon, M.M. & Partinen, M. 2002. Insomnia and global sleep dissatisfaction in Finland. Journal of Sleep Research 11, 339–346.

Ohayon, M.M. & Reynolds, C.F. 3rd. 2009. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Medicine 10(9), 952-960.

Oja, P., Laukkanen, R., Pasanen, M., Tyry, T. & Vuori, I. 1991. A 2-km walking test for assessing the cardiorespiratory fitness of healthy adults. International Journal of Sports Medicine 12(4), 356-362.

Paalasmaa, J., Waris, M., Toivonen, H., Leppäkorpi, L. & Partinen, M. 2012. Unobtrusive online monitoring of sleep at home. Conference Proceedings of IEEE Engineering in Medicine and Biology Society 2012, 3784-3788.

Pallesen, S., Sivertsen, B., Nordhus, I.H. & Bjorvatn, B. 2014. A 10-year trend of insomnia prevalence in the adult Norwegian population. Sleep Medicine 15, 173-179.

Palm, A., Janson, C. & Lindberg, E. 2015. The impact of obesity and weight gain on development of sleep problems in a population-based sample. Sleep Medicine 16, 593-597.

Pan, W. & Kastin, A.J. Leptin: a biomarker for sleep disorders? Sleep Medicine Reviews 18(3), 283-290.

Partinen, M. & Gislason, T. 1995. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. Journal of Sleep Research 4, 150-155.

Passos, G.S., Poyares, D., Santana, M.G., Garbuio, S.A., Tufik, S. & Mello, M.T. 2010. Effect of acute physical exercise on patients with chronic primary insomnia. Journal of Clinical Sleep Medicine 6(3), 270-275.

Passos, G.S., Poyares, D., Santana, M.G., et al. 2011. Effects of moderate aerobic exercise training on chronic primary insomnia. Sleep Medicine 12, 1018-1027.

Patel, S.R., Blackwell, T., Redline, S., Ancoli-Israel, S., Cauley, J.A., Hillier, T.A., Lewis, C.E., Orwoll, E.S., Stefanick, M.L., Taylor, B.C., Yaffe, K., Stone, K.L., Osteoporotic Fractures in Men Research Group, Study of Osteoporotic Fractures Research Group. 2008. The association between sleep duration and obesity in older adults. International Journal of Obesity (Lond) 32(12), 1825-1834.

Perron, I.J., Pack, A.I. & Veasey, S. 2015. Diet/Energy Balance Affect Sleep and Wakefulness Independent of Body Weight. Sleep 38(12), 1893-1903.

Phillips, F., Chen, C.N., Crisp, A.H., Koval, J., McGuinness, B., Kalucy, R.S., Kalucy, E.C. & Lacey, J.H. 1975. Isocaloric diet changes and electroencephalographic sleep. The Lancet 2(7938), 723-725.

Pigeon, W.R., Carr, M., Gorman, C. & Perlis, M.L. 2010. Effects of a tart cherry juice beverage on the sleep of older adults with insomnia: a pilot study. Journal of Medicinal Food 13(3), 579-583.

Pivik, R.T. & Busby, K. 1996. Heart rate associated with sleep onset in preadolescents. Journal of Sleep Research 5(1), 33-36.

Rajput, V. & Bromley, S.M. 1999. Chronic insomnia: a practical review. American Family Physician 60(5), 1431-1438, discussion 1441-1442.

Reid, K.J., Baron, K.G., Lu, B., Naylor, E., Wolfe, L. & Zee, P.C. 2010. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. Sleep Medicine 11, 934-940.

Riemann, D., Nissen, C., Palagini, L., Otte, A., Perlis, M.L. & Spiegelhalder, K. 2015. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurology 14(5), 547-558.

Riemann, D. & Spiegelhalder, K. 2014. Orexin receptor antagonists: a new treatment for insomnia? Lancet Neurology 13(5), 441-443.

Romero-Corral, A., Caples, S.M., Lopez-Jimenez, F. & Somers, V.K. 2010. Interactions between obesity and obstructive sleep apnea: implications for treatment. Chest 137(3), 711-719.

Rondanelli, M., Opizzi, A., Monteferrario, F., Antoniello, N., Manni, R. & Klersy, C. 2011. The effect of melatonin, magnesium, and zinc on primary insomnia in long-term care facility residents in Italy: a double-blind, placebo-controlled clinical trial. Journal of the American Geriatrics Society 59(1), 82-90.

Rosekind, M.R. & Gregory, K.B. 2010. Insomnia risks and costs: health, safety, and quality of life. American Journal of Managed Care 16(8), 617-626.

Roth, T., Coulouvrat, C., Hajak, G., Lakoma, M.D., Sampson, N.A., Shahly, V., Shillington, A.C., Stephenson, J.J., Walsh, J.K. & Kessler, R.C. 2011. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. Biological Psychiatry 69, 592-600.

Sateia, M.J. 2014. International classification of sleep disorders-third edition: highlights and modifications. Chest 146(5), 1387-1394.

Schäfer, H., Pauleit, D., Sudhop, T., Gouni-Berthold, I., Ewig, S. & Berthold, H.K. 2002. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest 122, 829-839.

Schenck, C.H., Mahowald, M.W. & Sack, R.L. 2003. Assessment and management of insomnia. The Journal of American Medical Association 289(19), 2475-2479.

Schwartz, M.W., Woods, S.C., Porte, D. Jr., Seeley, R.J. & Baskin, D.G. 2000. Central nervous system control of food intake. Nature 404 (6778), 661-671.

Schwartz, S., McDowell Anderson, W., Cole, S.R., Cornoni-Huntley, J., Hays, J.C. & Blazer, D. 1999. Insomnia and heart disease: a review of epidemiologic studies. Journal of Psychosomatic Research 47(4), 313-333.

Shechter, A., O'Keeffe, M., Roberts, A.L., Zammit, G.K., RoyChoudhury, A. & St-Onge, M.P. 2012. Alterations in sleep architecture in response to experimental sleep curtailment are associated with signs of positive energy balance. The American Journal of Physiology - Regulatory, Integrative and Comparative Physiology 303, R883-889.

Sherrill, D.L., Kotchou, K. & Quan, S.F. 1998. Association of physical activity and human sleep disorders. Archives of Internal Medicine 158(17), 1894-1898.

Shin, J.H., Chee, Y.J., Jeong, D.U. & Park, K.S. 2010. Nonconstrained sleep monitoring system and algorithms using air-mattress with balancing tube method. IEEE Transactions on Information Technology in Biomedicine 14(1), 147-156.

Smagula, S.F., Stone, K.L., Fabio, A. & Cauley, J.A. 2016. Risk factors for sleep disturbances in older adults: Evidence from prospective studies. Sleep Medicine Reviews 25, 21-30.

Spaeth, A.M., Dinges, D.F. & Goel, N. 2013. Effects of Experimental Sleep Restriction on Weight Gain, Caloric Intake, and Meal Timing in Healthy Adults. Sleep 36, 981-990.

St-Onge, M.P. 2013. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. Journal of Clinical Sleep Medicine 9(1), 73-80.

St-Onge, M.P., Roberts, A.L., Chen, J., Kelleman, M., O'Keeffe, M., RoyChoudhury, A. & Jones, P.J. 2011. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. American Journal of Clinical Nutrition 94, 410-416.

St-Onge, M.P., Roberts, A., Shechter, A. & Choudhury, A.R. 2016. Fiber and Saturated Fat Are Associated with Sleep Arousals and Slow Wave Sleep. Journal of Clinical Sleep Medicine 12(1), 19-24.

Sun, H., Kennedy, W.P., Wilbraham, D., Lewis, N., Calder, N., Li, X., Ma, J., Yee, K.L., Ermlich, S., Mangin, E., Lines, C., Rosen, L., Chodakewitz, J. & Murphy, G.M. 2013. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. Sleep 36(2), 259-267.

Tachibana, H., Izumi, T., Honda, S., Horiguchi, I., Manabe, E. & Takemoto, T. 1996. A study of the impact of occupational and domestic factors on insomnia among industrial workers of a manufacturing company in Japan. Occupational Medicine (Lond) 46(3), 221-227.

Taheri, S., Lin, L., Austin, D., Young, T. & Mignot, E. 2004. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Medicine 1(3), e62.

Tanaka, E., Yatsuya, H., Uemura, M., Murata, C., Otsuka, R., Toyoshima, H., Tamakoshi, K., Sasaki, S., Kawaguchi, L. & Aoyama, A. 2013. Associations of protein, fat, and carbohydrate intakes with insomnia symptoms among middle-aged Japanese workers. Journal of Epidemiology 23(2), 132-138.

The National Nutrition Council of Finland. 2005. Suomalaiset Ravitsemussuositukset – ravinto ja liikunta tasapainoon [The Finnish Nutrition Recommendations - nutrition and physical balance]. Helsinki: The National Nutrition Council of Finland.

Troxel, W.M., Buysse, D.J., Matthews, K.A., Kip, K.E., Strollo, P.J., Hall, M., Drumheller, O. & Reis, S.E. 2010. Sleep symptoms predict the development of the metabolic syndrome. Sleep 33(12), 1633-1640.

UKK Institute. 2006. UKK Walk Test: Tester's guide. Tampere: UKK Institute.

Vanitallie, T.B. 2006. Sleep and energy balance: Interactive homeostatic systems. Metabolism 55(10 Suppl 2), S30-35.

Wells, A.S., Read, N.W., Uvnas-Moberg, K. & Alster, P. 1997. Influences of fat and carbohydrate on postprandial sleepiness, mood, and hormones. Physiology and Behavior 61, 679-686.

Westerlund, A., Bellocco, R., Sundström, J., Adami, H.O., Åkerstedt, T. & Trolle Lagerros, Y. 2013. Sleep characteristics and cardiovascular events in a large Swedish cohort. European Journal of Epidemiology 28(6), 463-473.

Winkelman, J.W. 2015. Insomnia Disorder. New England Journal of Medicine 373 (15), 1437-1444..

Wu, M.P., Lin, H.J., Weng, S.F., Ho, C.H., Wang, J.J. & Hsu, Y.W. 2014. Insomnia subtypes and the subsequent risks of stroke: report from a nationally representative cohort. Stroke 45(5), 1349-1354.

Yamamura, S., Morishima, H., Kumano-go, T., Suganuma, N., Matsumoto, H., Adachi, H., Sigedo, Y., Mikami, A., Kai, T., Masuyama, A., Takano, T., Sugita, Y. & Takeda, M. 2009. The effect of Lactobacillus helveticus fermented milk on sleep and health perception in elderly subjects. European Journal of Clinical Nutrition 63(1), 100-105..

Yang, P.Y., Ho, K.H., Chen, H.C. & Chien, M.Y. 2012. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. Journal of Physiotherapy 58(3), 157-163.

Youngstedt, S.D. 2005. Effects of exercise on sleep. Clinics in Sports Medicine 24(2), 355-65, xi.

# ORIGINAL PUBLICATIONS

## I

**Effects of exercise and diet interventions on obesity-related sleep disorders in men: study protocol for a randomized controlled trial**

by

Tan X, Saarinen A, Mikkola TM, Tenhunen J, Martinmäki S, Rahikainen A, Cheng S, Eklund N, Pekkala S, Wiklund P, Munukka E, Wen X, Cong F, Wang X, Zhang Y, Tarkka IM, Sun Y, Partinen M, Alén M, Cheng S

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TRIALS

STUDY PROTOCOL Open Access

# Effects of exercise and diet interventions on obesity-related sleep disorders in men: study protocol for a randomized controlled trial

Xiao Tan[1], Antti Saarinen[2], Tuija M Mikkola[1], Jarkko Tenhunen[1], Samu Martinmäki[1], Aki Rahikainen[1], Shumei Cheng[1], Niklas Eklund[3], Satu Pekkala[1], Petri Wiklund[1], Eveliina Munukka[1], Xinfei Wen[1], Fengyu Cong[4], Xi Wang[5], Yajun Zhang[5], Ina Tarkka[1], Yining Sun[5], Markku Partinen[3], Markku Alen[6,7] and Sulin Cheng[1,5*]

## Abstract

**Background:** Sleep is essential for normal and healthy living. Lack of good quality sleep affects physical, mental and emotional functions. Currently, the treatments of obesity-related sleep disorders focus more on suppressing sleep-related symptoms pharmaceutically and are often accompanied by side effects. Thus, there is urgent need for alternative ways to combat chronic sleep disorders. This study will investigate underlying mechanisms of the effects of exercise and diet intervention on obesity-related sleep disorders, the role of gut microbiota in relation to poor quality of sleep and day-time sleepiness, as well as the levels of hormones responsible for sleep-wake cycle regulation.

**Methods/design:** Participants consist of 330 (target sample) Finnish men aged 30 to 65 years. Among them, we attempt to randomize 180 (target sample) with sleep disorders into exercise and diet intervention. After screening and physician examination, 101 men with sleep disorders are included and are randomly assigned into three groups: exercise (n = 33), diet (n = 35), and control (n = 33). In addition, we attempt to recruit a target number of 150 healthy men without sleep disorders as the reference group. The exercise group undergoes a six-month individualized progressive aerobic exercise program based on initial fitness level. The diet group follows a six month specific individualized diet program. The control group and reference group are asked to maintain their normal activity and diet during intervention. Measurements are taken before and after the intervention. Primary outcomes include objective sleep measurements by polysomnography and a home-based non-contact sleep monitoring system, and subjective sleep evaluation by questionnaires. Secondary outcome measures include anthropometry, body composition, fitness, sleep disorder-related lifestyle risk factors, composition of gut microbiota and adipose tissue metabolism, as well as specific hormone and neurotranmitter levels and inflammatory biomarkers from venous blood samples.

**Discussion:** It is expected that the improvement of sleep quality after exercise and diet intervention will be evident both in subjective and objective measures of quality of sleep. Additionally, the change of sleep quality induced by exercise and diet intervention is expected to be related to the changes in specific hormones and inflammatory biomarkers, and in the composition of gut microbiota.

**Trial registration:** Current Controlled Trials ISRCTN77172005

**Keywords:** Lifestyle intervention, Sleep disorders, Quality of sleep, Obstructive sleep apnea, Insomnia, Sleep measurement, Obesity, Gut microbiota, Neurotransmitters

* Correspondence: sulin.cheng@jyu.fi
[1]Department of Health Sciences, University of Jyväskylä, Rautpohjankatu 8, PO Box 35, 40700 Jyväskylä, Finland
[5]Institute of Intelligent Machines, Chinese Academy of Sciences, 350 Shushan Road, Hefei 230031, Anhui, People's Republic of China
Full list of author information is available at the end of the article

## Background

We spend one-third of our lifetime in sleep. Sleep is absolutely essential for maintaining healthy physical, mental and emotional functions. Sleep disorder impairs one's ability to think quickly, to work efficiently, and to associate freely, thus making one feel generally 'disconnected' from the world. In some serious cases, the sleep disorder-related conditions may lead to serious neurasthenia and depression [1,2]. Obesity is a major risk factor for sleep disorders, which may cause symptoms such as obstructive sleep apnea (OSA) [3,4]. OSA has an estimated prevalence of 2% to 4% among adults aged 30 to 60 years and the proportion is increasing [5,6]. OSA is associated with significant morbidity and mortality due to accidents, cardiovascular diseases, and stroke [7,8]. In addition, insomnia is a common sleep disorder that impairs quality of life from both physiological and psychological aspects, with prevalence range from 10% to 40% in Western countries [9-11]. Besides insomnia, a considerable proportion of the general adult population reports chronic mild to moderate sleep complaints which result in long-term poor quality of sleep, as well as increased health care visits [12].

Two thirds of middle-aged sleep apneic men are obese, and visceral obesity has been observed to be a primary risk factor for OSA [7]. Obesity reflected by body weight and body mass index (BMI) is also related to poor subjective quality of sleep [13] and short sleep duration [14-18] among adults. A widely supported theory that obesity induces inflammatory reactions may explain the association between obesity and sleep disorders [19,20]. Elevated levels of inflammatory biomarkers, such as C-reactive protein (CRP) [21,22], interleukin-6 (IL-6) [22,23], and tumor necrosis factor-alpha (TNF-alpha) [24] are reported among OSA patients. People with non-apneic sleep disorders also demonstrate changed levels of inflammatory biomarkers [25-27]. Both short or excessive habitual sleep duration are linked with greater levels of CRP [25-27], while short sleep duration recoded by polysomnography (PSG) is related to higher levels of TNF-alpha [25]. However, it is still unclear whether inflammation causes sleep disorders or vice versa [28-31].

Sleep disorders elevate the risk of obesity by affecting eating patterns and other lifestyle factors. Short sleep duration is associated with higher energy intake, mostly due to increased consumption of saturated fat [32]. Weight loss from three months exercise training or one year diet control alleviates the symptom of OSA by lowering the apnea-hypopnea index (AHI) [33-35]. The possible association between weight loss and subjective quality and quantity of sleep is exhibited in some adult women [36]. Despite the change of body weight and BMI, lifestyle intervention through aerobic or resistance exercise may improve quality of sleep in middle-aged and older adults with sleep complaints [9,12]. However, more clinical trials are needed since very few previous studies have utilized objective sleep measurements [32,37].

Gut microbiota is suggested to act as an important factor regulating adipose metabolism, and affecting neurological functions. Animal studies show that gut microbiota affects energy harvest from diet and energy storage in the host. The association is reflected by lower metabolic rate, increased hepatic production of triglycerides, and promoted storage of triglycerides in adipocytes among mice with gut microbiota compared with their germ-free counterparts [38]. In human studies, composition of gut microbiota shows differences between obese and lean subjects [39], and certain types of gut microbiota may independently link to obesity-related metabolic disorder [40]. Moreover, gut microbiota may be involved in modulation of both central and peripheral nerve function, such as the hypothalamus-pituitary-adrenal (HPA) axis and thus associate with neuropsychiatric conditions including anxiety, depression, and sleep disorders [41,42]. Composition of gut microbiota can be altered through long-term dietary intervention [43]; however whether changing the human intestinal microbiota through lifestyle intervention helps to mediate sleep disorders has yet to be studied.

### Methods/design

The study aims to involve 330 Finnish men aged 30 to 65 years with or without sleep disorders. Participants are recruited from City of Jyväskylä health care centers in the Central Finland Health Care District and its surroundings via doctors' referral and advertising in news media and on the internet between 28 April 2011 and 2 April 2013. Among the total 330 target number of participants, 180 are sleep disordered with OSA or insomnia (OSA is diagnosed and referred by a sleep specialist physician at the Central Hospital of Central Finland prior to the baseline assessments. Insomnia is reported first by the participants then examined by a physician prior to other baseline assessments. The definition of insomnia is based on the following symptoms: recurrent difficulty in falling asleep, too short sleep duration or poor quality of sleep during the previous three months [44]). The remaining 150 participants are healthy men without sleep disorders.

Among the 180 men with sleep disorders, 171 responded to the initial advertisement (response rate: 95%). A screening interview was carried out for interested participants who contacted the researchers. The screening covered the participant's health and medical conditions and certain lifestyle factors such as physical activity, type of employment, and so on. Sixty-six participants did not meet the inclusion criteria. The remaining 105 participants were invited to the laboratory and evaluated

by a physician to make sure that they could be included in the intervention study. The examination by a physician included cardiac and musculoskeletal status evaluations, risk evaluation concerning exercise tolerance [45], and family background-related diseases, through which four participants were excluded. Thereafter, baseline tests were performed. Participants with sleep disorders were randomized into three groups: exercise, diet, and control. The exercise and diet groups followed a six-month guided individualized exercise and diet counseling intervention program respectively, while the control group and reference group members were asked to maintain their current life habits. Measurements were carried out before and after intervention, and in addition, some variables were also measured at the three-month time point.

A target number of 150 healthy participants have been continuously recruited. All healthy participants in the initial contact have to pass the same evaluations as their sleep disordered counterparts. After the baseline assessments, a subgroup of the healthy participants are asked to participate in the same extensive sleep measurements and follow-up tests as the apnea group in order to serve as a reference group (target n = 12).

The trial is registered under www.controlled-trials.com: ISRCTN77172005. A summary of the study design is presented in Figure 1.

## Hypotheses

1. Physical activity is beneficial in terms of good quality and proper duration of sleep. The levels of melatonin, cortisol, and neuro-active steroids are modified by physical activity and thereby influence sleep.

2. The amount of micronutrients in the diet, such as tryptophan and the vitamin Bs, are correlated with quality and duration of sleep.

3. Six-month guided individualized exercise or diet counseling intervention can independently alleviate sleep disorders among adult men with sleep disorders. The improvement can be observed by changes in duration of total sleep, duration and proportion of slow-wave sleep (SWS) and rapid eye movement (REM) sleep, stress reactions based on heart rate variability (HRV) and AHI (participants with OSA), as well as subjective sleep measures such as the Epworth Sleepiness Scale score.

4. Prolonged good quality of sleep after six-month individualized exercise intervention is linked to decreased oxidative stress that in turn may affect melatonin levels in the peripheral circulation because indole is rapidly used to combat free radical damage. Exercise also affects cortisol and neuro-active steroid levels. The mutual interactions between exercise and these hormonal milieus are responsible for sleep-wake cycle regulation.

5. Six-month guided individualized exercise and diet counseling intervention can improve sleep quality through modification of gut microbiota composition. The composition of the gut microbial community is host-specific, evolving throughout an individual's lifetime and susceptible to both exogenous and endogenous modifications. Hence, the cross-talk between gut hormones and hypothalamic factors (gut-brain axis) is important in the regulation of food intake and sleep disorders.

## Primary and secondary outcomes

### *Primary endpoints*

Duration and proportion of sleep stages, heart rate, heart rate variability, respiration and body movements during sleep, and AHI (PSG for participants with OSA;pressure sensor measurement for both OSA and other participants)

Subjective measures of duration and quality of sleep (Nordic sleep disorder questionnaire, Epworth Sleepiness Scale, seven-day sleep diary)

Lifestyle risk clusters related to sleep disorders (healthy versus sleep disordered patients)

### *Secondary endpoints*

Anthropometry (body weight and height; waist, hip, chest and neck circumferences)

Blood pressure

Body composition (dual-energy x-ray absorptiometry and bioimpedance)

Fitness (2 km walking test, three-minute step test)

Composition of gut microbes (fecal sample)

Subcutaneous adipose tissue metabolism (total RNA)

Venous blood samples (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, histamine, tryptophan, melatonin, cortisol, adrenalin, leptin, adiponectin, neuro-active steroids, fatty acids, B vitamins, fatty acid profile, and inflammatory variables such as CRP, IL-6, TNF-alpha, and so on)

## Participants

Participants in this study consist of a target sample of 330 Finnish men aged 30 to 65 years.

Participants with sleep disorders: a target number of 180 men with sleep disorders are to be randomized into exercise or diet intervention groups. After screening and physician examination, 35 men with diagnosed mild to moderate OSA and 66 with insomnia confirmed by a physician have been included.

Inclusion criteria for apnea and insomnia patient groups:

- Men in an age range of 30 to 65 years
- Occasionally physically active or sedentary (regular leisure-time exercise ≤ two times per week and ≤ 45 minutes per session)

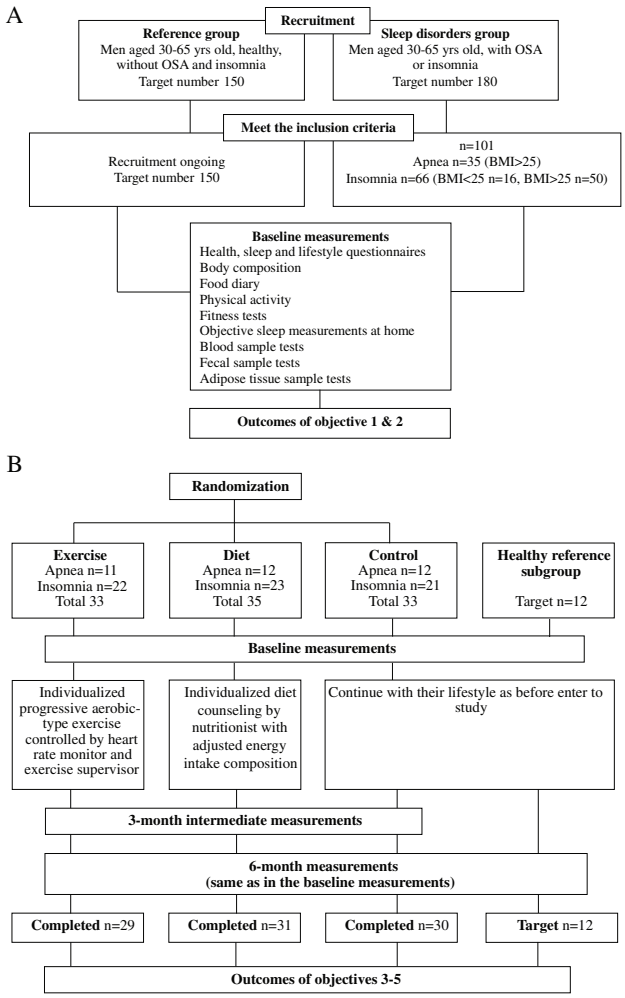


**Figure 1 Flow diagram of the study design. (A)** study design summary of objectives 1 and 2; **(B)** study design summary of objectives 3 to 5.

- Report recurrent difficulty in falling asleep, too short sleep duration or poor quality of sleep during past two months, or with mild to moderate OSA (AHI 5 to 30/hour) with or without continuous positive airway pressure (CPAP) treatment. If under treatment, nasal CPAP for a minimum period of six months prior to the baseline measurements, with a minimum adherence to CPAP therapy for four hours per night
- Relatively healthy (free from cardiovascular comorbidities)

Exclusion criteria:

- Diseases and medications related to: insulin dependent diabetes mellitus, Crohn's disease, sarcoidosis, celiac disease, thyroid, liver and severe heart diseases, chronic diarrhea, ulcerative colitis,

rheumatoid arthritis, severe osteoarthritis, systemic lupus erythematosus, and cancer during the past three years
- Currently taking a special diet (such as a very low calorie diet)
- Other diagnosed sleep disorders (such as narcolepsy)
- Shift workers (working during the night)
- Reported cognitive impairment
- Using antibiotics during the previous three months
- History of eating disorders
- Participants using CPAP, professional drivers and other professions that are at risk of accidents due to discontinuation in CPAP treatment
- Not suitable for the study by a physician's evaluation

Healthy participants: a target number of 150 healthy men without sleep disorders are intended to be recruited as the reference group. Sixty-three overweight/obese (BMI from >25 to <38) and 44 normal body weight (BMI <25) men with no diseases and taking no medications have been included so far.

Inclusion criteria for reference (healthy men) group:

- Men in an age range of 30 to 65 years
- No chronic sleep disorders and taking no medications related to sleep disorders
- No disease and medications during past one year
- Relatively healthy (free from cardiovascular comorbidities)

Exclusion criteria for reference (healthy men) group are the same as for the patient group.

#### Randomization

The apnea and insomnia patients are randomized into the following groups using case-matched computer-generated random number according the participants enrollment order:

Exercise intervention group, n = 33 (apnea = 11 and insomnia = 22)

Diet intervention group, n = 35 (apnea = 12 and insomnia = 23)

Control group, n = 33 (apnea = 12 and insomnia = 21).

#### Exercise intervention

In this study, exercises are selected as a combination of Nordic walking, stretching, strength, and relaxation. An individual progressive exercise program, based on the fitness test result at the baseline, is set up in a wrist computer (M5, Suunto Oy, Valimontie 7, 01510 Vantaa, Finland). The exercise is supervised by a specialized trainer once a week and the participants follow the guided exercise program three to five times per week, 30 to 60 minutes per session, at the level of 60 to 75% of the maximum heart rate. The participants transfer their exercise data to the study server via the internet. The participants' performance is checked and their exercise program updated once a month by the trainer. Each participant has an individual account which is only accessible by him and by the coordinator and researchers of the study. The guided individualized exercise training program is planned to last for six months (26 weeks).

#### Diet intervention

Specific individualized diet programs are developed after baseline assessments of each participant's current dietary intakes (based on three-day food diary) and body weight. Dietary suggestions are given to each individual through group and individual face-to-face counseling during the intervention. The suggested diet contains energy of 40% carbohydrate with < 5% sucrose, 40% fat (saturated fatty acid (SAFA) 10%, monounsaturated fatty acid (MUFA) 15– to 20%, polyunsaturated fatty acid (PUFA) 10%) and 20% protein. In addition, a rich source of vitamins and other micronutrients such as calcium, magnesium, potassium, folate, pyridoxine, cobalamin and choline is also recommended in the guidance. Overweight/obese participants are advised to moderately reduce their total energy intake (by 300 to 500 kcal per day for the first three months) with guidance on the proportion of macronutrients to be consumed. The target is to reduce body weight by 3 kg in the first three months of the intervention. After this period, the participants are advised to maintain their achieved body weight reduction, and continue to gradually reduce their body weight towards normal levels, with a target of a 10% reduction from their initial body weight. Participants with normal weight are advised to maintain their body weight.

Diet intervention is controlled by various methods. An online nutritional counseling service (MealTracker) is used in this study. Participants are asked to send photos of all food intakes during one day to the service 1 to 2 days a week (randomly selected by researcher). The photos are sent by cellphone (mobile application) or computer (MealTracker website, www2.mealtracker.fi). The study nutritionist analyzes dietary composition through the photos uploaded and gives feedback via text messages or E-mail to each participant weekly during the first month, and monthly during the rest of intervention. Each participant has an individual account on the server which was only accessible by himself, nutritionists, and researchers of the study. Food diary information is also collected at the three-month time point in order to give more dietary suggestions. Moreover, there are two opportunities for each participant in the dietary intervention group to attend cooking lessons. The cooking lessons are held during the first and second three months of the intervention, respectively. Each time, five or six participants are

taught by the nutritionist to cook food that meets the nutritional criteria of this study, and to exchange dietary information.

### Control group

The control group members are asked to maintain their normal activity and diet during the intervention. After the intervention has finished, they are provided with the opportunity of taking three months simultaneous exercise and dietary counseling following the same protocol as the intervention groups.

### Study examinations

All the measurements are carried out before and after six months intervention at the Laboratory of Sport and Health Sciences, University of Jyväskylä. In addition, sleep questionnaire and fitness measurements are also carried out at three months. The measurements are listed below.

Background information regarding lifestyle as well as medical history is collected by questionnaire. Data gathered from eligible participants is used to describe the study populations. Data on self-evaluation of sleep disorders is collected by using the Nordic sleep disorder questionnaire, Epworth Sleepiness Scale as well as a sleep diary [46,47]. Daily physical activities are recorded before, during and after intervention up to seven days for type and duration of all physical activities.

A three-day food diary (two working days and one weekend day) is recorded by all participants. The diary includes type and estimated amount of all food and drink intake during each day. The food records contain time of eating, items and portion of food. Details of all foodstuffs, dishes and drinks including the type and commercial brand name were filled in the records. All the food consumption data are coded into a nutrition program. The mean daily food consumption by main groups and the energy and nutrient intakes are calculated using a Micro-Nutrica software PCprogram developed and maintained by the Research Center of the Social Insurance Institution, Finland (Nordenskiöldinkatu 12, 00250 Helsinki, Finland) [48]. The Micro-Nutrica database contains 66 dietary factors, 680 different food items, and about 640 dishes commonly consumed in Finland.

Health condition examination: a physician examines the physical condition of participants and checks their health history and medications to ensure they meet the inclusion criteria for the study.

Anthropometry and body composition assessments: height and weight are measured and used to determine body mass index (BMI, weight(kg)/height$^2$(m)). Chest, waist, hip and neck circumference are measured by using a measuring tape in the conventional way. Blood pressure is measured after five minutes rest. Lean mass, fat mass and bone mass of the whole body are assessed by using dual-energy X-ray densitometry (DXA Prodigy, GE Lunar, OH, USA).

Venous blood samples are taken in standardized fasting conditions in the morning between 7 and 9 am. Serum samples are kept frozen at −80°C until assayed. Biochemical assessments include total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, glucose, insulin, histamine, tryptophan, melatonin, cortisol, adrenalin, leptin, adiponectin, neuro-active steroids, fatty acids, B vitamins and hormones.

Fecal samples are collected by participants at home with tools provided by the study group, under detailed instruction. The samples are stored at −20°C after collection until assayed. The composition of microbiota is measured by using 16S rRNA-hybridization and DNA-staining.

Subcutaneous adipose tissue samples are taken from a subgroup at the waist by a physician. Total RNA is extracted by using the Trizol method (Life Technologies Corporation, 5791 Van Allen Way, Carlsbad, CA 92008, USA). Reverse transcription reaction followed by real-time PCR with gene-specific primer sequences is carried out.

Fitness test: two types of fitness tests are performed: UKK 2 km Walk Test and YMCA Step Test, with a one-hour rest between the two tests. The UKK Walk Test is performed by walking two kilometers as fast as possible on a flat surface [49]. The result is recorded as a fitness index. This index is used to determine the individualized exercise program for those in the exercise group. Both tests are safe for obese people and well represent their fitness level.

Polysomnography (PSG measurements including, for example, EEG, EOG, EMG, movement, ECG and transcutaneous carbon dioxide) is used to evaluate sleep stages and quality, including the non-rapid eye movement (NREM) and rapid eye movement (REM) sleep in all OSA participants in their homes. In addition, seven-night sleep measurements both before and after intervention are taken for all participants by using a non-contact sleep monitoring system at their homes (Beddit sleep tracker, Beddit.com Oy, Kimmeltie 3, 02110 Espoo, Finland) [50]. The measurement records are sent automatically to the Beddit server via the internet, where sleep analyses including sleep stages, HRV and stress reactions are carried out simultaneously. The possible conditions which may affect the measurement, such as children and pets in the bedroom are recorded in the sleep diary. A research assistant visits each participant's home to set up the system before measurements start.

OSA patients using nasal CPAP are required to stop the treatment for seven days before the PSG sleep measurement. After the baseline measurement, all the patients can continue their regular CPAP therapy for the next six months. After six months of nasal CPAP therapy

and intervention, all the patients again stop using their CPAP for seven days before the follow-up PSG measurement. Stopping using CPAP treatment for seven days has no risk for mild and moderate OSA patients, and this is ensured by the physicians who have sufficient experience of OSA treatments and research. Moreover, if the participant experiences intense tiredness due to the discontinuation of CPAP, the PSG measurement is arranged after a shorter discontinuation period.

## Discussion

Currently there is a lack of evidence regarding the associations between lifestyle, metabolism, and sleep. This study focuses on middle-aged men with two different sleep disorders; OSA and insomnia. Through a six-month intervention with either aerobic exercise or optimized diet, results from a range of sleep assessments will provide a clear information about differences in sleep duration, sleep stages, and quality of sleep among the different groups. A comparison between subjective sleep evaluation and objective sleep measurement results among sleep disordered men will also be possible with the data from this study. Variables in the physiological dimension are important references for explaining mechanisms behind sleep and lifestyle. Measurements of neurotransmitters, gut microbiota composition, and adipose tissue characteristics before and after intervention in this trial may strengthen evidence for links between lipid metabolism and sleep outcomes, or find new associations in related fields.

Comparing the participants who have sleep disorders to their healthy counterparts will allow us to find out which lifestyle risk factors are associated with sleep quality and duration. The detailed information collected in this study regarding levels of physical activity and different composition of food intakes and micronutrients will be used to test our hypotheses 1 and 2. This information can be used for diagnosing risk factors and developing healthcare guidance related to sleep disorders.

In this study we applied modern technology combined with socio-psychological support and self-commitment to ensure the participants' compliance during the intervention. The online exercise diary service and remote food analysis and counseling have been rarely, if ever, used in previous studies and thus may enhance the efficacy and reliability of the intervention. We believe that allowing participants to monitor their progress more effectively could be a potent tool in helping them to change inactive and unhealthy lifestyles.

The current burden of sleep disorders is associated with sedentary lifestyles and unhealthy diets [37,51]. In Finland, great effort has been made to use exercise and dietary intervention to prevent chronic disease clusters and reduce the related socio-economic burden, such as in the context of cardiovascular disease [52]. This study is expected to provide abundant experimental and cross-sectional results, which may shed light on many aspects of sleep and metabolism and the interaction between the two.

### Ethical and data protection issues

The study is approved by the Ethic Committee of the Central Finland Health Care District (7/2011 OTE). Participants in this study are volunteers. None of the measurements are known to entail any significant health risk. The study has its own physician to ensure the eligibility and safety of participants. All data are handled and archived confidentially and are registered with the Finnish National Data Protection Ombudsman. The benefits and associated risks of the study are carefully explained and the voluntary nature of the participation is emphasized. Informed consent is obtained from all participants prior the baseline measurements. If the participant agreed to participate, a copy of the signed consent form is kept in his records.

### Trial status

Participant recruitment for intervention started in April 2011. Baseline measurements were taken between June and December 2011, and all six-month exercise and diet interventions with follow-up measurements for the intervention groups were completed by July 2012. Participants in the control group who attended the extra three-month exercise plus diet intervention finished the follow-up measurements by January 2013. Feedback meetings for participants have been held twice to explain the preliminary results of their health and sleep quality after the completion of intervention. Biomarker assays of the study are continuously under analyses. The recruitment of the healthy reference group started from June 2012 and will be completed by April 2013. Feedback for the healthy participants is planned to be given during June and July 2013.

#### Abbreviations

AHI: apnea hypopnea index; BCG: ballistocardiography; BMI: body mass index; CPAP: continuous positive airway pressure; CRP: C-reactive protein; CVD: cardiovascular disease; ECG: electrocardiography; HPA axis: hypothalamic-pituitary-adrenal axis; HRV: heart rate variability; IL-6: interleukin-6; MUFA: monounsaturated fatty acid; NREM: non-rapid eye movement; OSA: obstructive sleep apnea; PCR: polymer chain reaction; PSG: polysomnography; PUFA: polyunsaturated fatty acid; REM: rapid eye movement; SAFA: saturated fatty acid; SWS: slow-wave sleep; TNF-alpha: tumor necrosis factor-alpha.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

CS is the principle investigator of the study and has full access to all of the data in the study and takes full responsibility for the integrity of the data and for the accuracy of the data analysis. None of the authors have financial or personal interest affiliations with the sponsors of this research effort. Study

concept and design: CS, TX, MTM, PM and AM. Acquisition of data: TX, SA, MTM, TJ, MS, RA, CSM, PS, WP, ME, WXF, AM and CS. Analysis and interpretation of data: TX, SA, MTM, CSM, EN, TJ, MS, PS, WP, ME, WXF, CFY, WX, ZYJ, TI, SYN, PM, AM and CS. Drafting of the manuscript: TX, MTM and CS. Critical revision of the manuscript for important intellectual content: TX, SA, MTM, CSM, TJ, MS, RA, EN, PS, WP, ME, WXF, CFY, WX, ZYJ, TI, SYN, PM, AM and CS. Funding obtaining: CS, SYN and AM. Administrative, technical, or material support: CSM, MTM, TJ, MS, RA, PS, SYN, AM and CS. Supervision: CS, CFY, TI, SYN and AM. All authors read and approved the final manuscript.

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**Author details**
[1]Department of Health Sciences, University of Jyväskylä, Rautpohjankatu 8, PO Box 35, 40700 Jyväskylä, Finland. [2]Central Finland Central Hospital, Central Finland Health Care District, Keskussairaalantie 19, 40620 Jyväskylä, Finland. [3]Helsinki Sleep Clinic, Vitalmed Research Center, Sitratori 3, Third floor, 00420 Helsinki, Finland. [4]Department of Mathematical Information Technology, University of Jyväskylä, (Agora), PO Box 35, 40014 Jyväskylä, Finland. [5]Institute of Intelligent Machines, Chinese Academy of Sciences, 350 Shushan Road, Hefei 230031, Anhui, People's Republic of China. [6]Department of Medical Rehabilitation, Oulu University Hospital, Oulu, Finland. [7]Institute of Health Sciences, University of Oulu, Kajaanintie 50, Oulu 90220, Finland.

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**References**

1. Morriss RK, Wearden AJ, Battersby L: **The relation of sleep difficulties to fatigue, mood and disability in chronic fatigue syndrome.** *J Psychosom Res* 1997, **42**(6):597–605.
2. Fava M: **Daytime sleepiness and insomnia as correlates of depression.** *J Clin Psychiatry* 2004, **65**(Suppl 16):27–32.
3. Vgontzas AN: **Does obesity play a major role in the pathogenesis of sleep apnea and its associated manifestations via inflammation, visceral adiposity, and insulin resistance.** *Arch Physiol Biochem* 2008, **114**(4):211–223.
4. Barcelo A, Barbe F, Llompart E, Mayoralas LR, Ladaria A, Bosch M, Agusti AG: **Effects of obesity on C-reactive protein level and metabolic disturbances in male patients with obstructive sleep apnea.** *Am J Med* 2004, **117**(2):118–121.
5. Panossian LA, Avidan AY: **Review of sleep disorders.** *Med Clin North Am* 2009, **93**(2):407–425.
6. Alves ES, Lira FS, Santos RV, Tufik S, de-Mello MT: **Obesity, diabetes and OSAS induce of sleep disorders: exercise as therapy.** *Lipids Health Dis* 2011, **10:**148.
7. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP: **Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia.** *J Clin Endocrinol Metab* 2000, **85**(3):1151–1158.
8. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V: **Obstructive sleep apnea as a risk factor for stroke and death.** *N Engl J Med* 2005, **353**(19):2034–2041.
9. Yang PY, Ho KH, Chen HC, Chien MY: **Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review.** *J Physiother* 2012, **58**(3):157–163.
10. Morin CM, LeBlanc M, Daley M, Gregoire JP, Mérette C: **Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors.** *Sleep Med* 2006, **7**(2):123–130. Epub 2006 Feb 3.
11. Ohayon MM, Partinen M: **Insomnia and global sleep dissatisfaction in Finland.** *J Sleep Res* 2002, **11**(4):339–346.
12. King AC, Pruitt LA, Woo S, Castro CM, Ahn DK, Vitiello MV, Woodward SH, Bliwise DL: **Effects of moderate-intensity exercise on polysomnographic and subjective sleep quality in older adults with mild to moderate sleep complaints.** *J Gerontol A Biol Sci Med Sci* 2008, **63**(9):997–1004.
13. Algul A, Ates MA, Semiz UB, Basoglu C, Ebrinc S, Gecici O, Gülsün M, Kardesoglu E, Cetin M: **Evaluation of general psychopathology, subjective sleep quality, and health-related quality of life in patients withobesity.** *Int J Psychiatry Med* 2009, **39**(3):297–312.
14. Patel SR, Blackwell T, Redline S, Ancoli-Israel S, Cauley JA, Hillier TA, Lewis CE, Orwoll ES, Stefanick ML, Taylor BC, Yaffe K, Stone KL, Osteoporotic Fractures in Men Research Group, Study of Osteoporotic Fractures Research Group: **The association between sleep duration and obesity in older adults.** *Int J Obes (Lond)* 2008, **32**(12):1825–1834. Epub 2008 Oct 21.
15. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB: **Inadequate sleep as a risk factor for obesity: analyses of the NHANES I.** *Sleep* 2005, **28**(10):1289–1296.
16. Chaput JP, Després JP, Bouchard C, Tremblay A: **The association between short sleep duration and weight gain is dependent on disinhibited eating behavior in adults.** *Sleep* 2011, **34**(10):1291–1297.
17. St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, Roychoudhury A, Jones PJ: **Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals.** *Am J Clin Nutr* 2011, **94**(2):410–416. Epub 2011 Jun 29.
18. Taheri S, Lin L, Austin D, Young T, Mignot E: **Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index.** *PLoS Med* 2004, **1**(3):e62. Epub 2004 Dec 7.
19. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB: **Elevated C-reactive protein levels in overweight and obese adults.** *JAMA* 1999, **282**(22):2131–2135.
20. Cancello R, Clément K: **Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue.** *BJOG* 2006, **113**(10):1141–1147. Epub 2006 Aug 10.
21. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK: **Elevated C-reactive protein in patients with obstructive sleep apnea.** *Circulation* 2002, **105**(21):2462–2464.
22. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T, Adachi M: **Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure.** *Circulation* 2003, **107**(8):1129–1134.
23. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbaro MP, Gramiccioni E, Barnes PJ: **Increased 8-isoprostane and interleukin-6 in breath condensate of obstructive sleep apnea patients.** *Chest* 2002, **122**(4):1162–1167.
24. Entzian P, Linnemann K, Schlaak M, Zabel P: **Obstructive sleep apnea syndrome and circadian rhythms of hormones and cytokines.** *Am J Respir Crit Care Med* 1996, **153**(3):1080–1086.
25. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, Redline S: **Sleep duration and biomarkers of inflammation.** *Sleep* 2009, **32**(2):200–204.
26. Williams CJ, Hu FB, Patel SR, Mantzoros CS: **Sleep duration and snoring in relation to biomarkers of cardiovascular disease risk among women with type 2 diabetes.** *Diabetes Care* 2007, **30**(5):1233–1240. Epub 2007 Feb 23.
27. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM: **Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk.** *J Am Coll Cardiol* 2004, **43**(4):678–683.
28. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S: **Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation.** *Arch Intern Med* 2006, **166**(16):1756–1762.
29. Pickup JC: **Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes.** *Diabetes Care* 2004, **27**(3):813–823.
30. Wang Z, Nakayama T: **Inflammation, a link between obesity and cardiovascular disease.** *Mediators Inflamm* 2010, **2010:**535918. Epub 2010 Aug 5.
31. Rohleder N, Aringer M, Boentert M: **Role of interleukin-6 in stress, sleep, and fatigue.** *Ann N Y Acad Sci* 2012, **1261:**88–96.
32. Patel SR, Hu FB: **Short sleep duration and weight gain: a systematic review.** *Obesity (Silver Spring)* 2008, **16**(3):643–653. Epub 2008 Jan 17.
33. Kline CE, Crowley EP, Ewing GB, Burch JB, Blair SN, Durstine JL, Davis JM, Youngstedt SD: **The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial.** *Sleep* 2011, **34**(12):1631–1640.
34. Tuomilehto HP, Seppä JM, Partinen MM, Peltonen M, Gylling H, Tuomilehto JO, Vanninen EJ, Kokkarinen J, Sahlman JK, Martikainen T, Soini EJ, Randell J, Tukiainen H, Uusitupa M, Kuopio SleepApnea Group: **Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea.** *Am J Respir Crit Care Med* 2009, **179**(4):320–327. Epub 2008 Nov 14.

35. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, Wadden TA, Kelley D, Wing RR, Pi-Sunyer FX, Reboussin D, Kuna ST, Sleep AHEAD Research Group of Look AHEAD Research Group: **A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study.** *Arch Intern Med* 2009, **169**(17):1619–1626.
36. Thomson CA, Morrow KL, Flatt SW, Wertheim BC, Perfect MM, Ravia JJ, Sherwood NE, Karanja N, Rock CL: **Relationship between sleep quality and quantity and weight loss in women participating in a weight-loss intervention trial.** *Obesity (Silver Spring)* 2012, **20**(7):1419–1425. Epub 2012 Mar 8.
37. Peuhkuri K, Sihvola N, Korpela R: **Diet promotes sleep duration and quality.** *Nutr Res* 2012, **32**(5):309–319. Epub 2012 Apr 25.
38. Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI: **The gut microbiota as an environmental factor that regulates fat storage.** *Proc Natl Acad Sci USA* 2004, **101**(44):15718–15723. Epub 2004 Oct 25.
39. DiBaise JK, Zhang H, Crowell MD, Krajmalnik-Brown R, Decker GA, Rittmann BE: **Gut microbiota and its possible relationship with obesity.** *Mayo Clin Proc* 2008, **83**(4):460–469.
40. Munukka E, Wiklund P, Pekkala S, Völgyi E, Xu L, Cheng S, Lyytikäinen A, Marjomäki V, Alen M, Vaahtovuo J, Keinänen-Kiukaanniemi S, Cheng S: **Women with and without metabolic disorder differ in their gut microbiota composition.** *Obesity (Silver Spring)* 2012, **20**(5):1082–1087. Epub 2012 Jan 30.
41. Fetissov SO, Déchelotte P: **The new link between gut-brain axis and neuropsychiatric disorders.** *Curr Opin Clin Nutr Metab Care* 2011, **14**(5):477–482.
42. Forsythe P, Sudo N, Dinan T, Taylor VH, Bienenstock J: **Mood and gut feelings.** *Brain Behav Immun* 2010, **24**(1):9–16. Epub 2009 May 28.
43. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD: **Linking long-term dietary patterns with gut microbial enterotypes.** *Science* 2011, **334**(6052):105–108. Epub 2011 Sep 1.
44. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M: **Clinical guideline for the evaluation and management of chronic insomnia in adults.** *J Clin Sleep Med* 2008, **4**(5):487–504.
45. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, American College of Sports Medicine: **American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise.** *Med Sci Sports Exerc* 2011, **43**(7):1334–1359.
46. Partinen M, Gislason T: **Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints.** *J Sleep Res* 1995, **4**(S1):150–155.
47. Johns MW: **A new method for measuring daytime sleepiness: the Epworth sleepiness scale.** *Sleep* 1991, **14**(6):540–545.
48. Rastas M, Seppänen R, Knuts LR, Karvetti RL, Varo P: *Ruokien ravintoainesisälto (Nutrient Composition of Foods)*. Turku: Kansaneläkelaitos; 1997.
49. Laukkanen R, Oja P, Pasanen M, Vuori I: **Validity of a two kilometer walking test for estimating maximal aerobic power in overweight adults.** *Int J Obes Relat Metab Disord* 1992, **16**(4):263–268.
50. Paalasmaa J, Waris M, Toivonen H, Leppäkorpi L, Partinen M: **Unobtrusive online monitoring of sleep at home**. In *Proceedings of the The 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society: 28 August- 1 September*. San Diego; 2012.
51. Yang CY, Chiou AF: **Predictors of sleep quality in community-dwelling older adults in Northern Taiwan.** *J Nurs Res* 2012, **20**(4):249–260.
52. Länsimies-Antikainen H, Pietilä AM, Laitinen T, Kiviniemi V, Rauramaa R: **Is informed consent related to success in exercise and diet intervention as evaluated at 12 months?DR's EXTRA study.** *BMC Med Ethics* 2010, **11**:9.

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# II

## Associations of disordered sleep with body fat distribution, physical activity and diet among overweight middle-aged men

by

Tan X, Alén M, Cheng SM, Mikkola TM, Tenhunen J, Lyytikäinen A, Wiklund P, Cong F, Saarinen A, Tarkka IM, Partinen M, Cheng S

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# Associations of disordered sleep with body fat distribution, physical activity and diet among overweight middle-aged men

XIAO TAN[1], MARKKU ALÉN[1,2], SHU MEI CHENG[1], TUIJA M. MIKKOLA[1], JARKKO TENHUNEN[1], ARJA LYYTIKÄINEN[3], PETRI WIKLUND[1], FENGYU CONG[4], ANTTI SAARINEN[3], INA TARKKA[1], MARKKU PARTINEN[5] and SULIN CHENG[1,6]

[1]Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland; [2]Department of Medical Rehabilitation, Oulu University Hospital and Institute of Health Sciences, University of Oulu, Oulu, Finland; [3]Central Hospital of Central Finland, Jyväskylä, Finland; [4]Department of Biomedical Engeneering, Dalian University of Technology, Dalian, Liaoning, China; [5]Helsinki Sleep Clinic, Vitalmed Research Center, Helsinki, Finland and [6]Department of Sport and Physical Education, Shanghai Jiao Tong University, Shanghai, China

**Keywords**
insomnia, OSA, comorbid insomnia and OSA, fat distribution, physical activity, dietary intakes

**Correspondence**
Sulin Cheng, University of Jyväskylä, PO Box 35, 40014 Jyväskylä, Finland.
Tel.: +358 40 8054122;
fax: +358 14 260 2001;
e-mail: sulin.cheng@jyu.fi

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**SUMMARY**

This cross-sectional study aimed to investigate whether body fat distribution, physical activity levels and dietary intakes are associated with insomnia and/or obstructive sleep apnea among overweight middle-aged men. Participants were 211 Finnish men aged 30–65 years. Among the 163 overweight or obese participants, 40 had insomnia only, 23 had obstructive sleep apnea only, 24 had comorbid insomnia and obstructive sleep apnea and 76 were without sleep disorder. The remaining 48 participants had normal weight without sleep disorder. Fat mass, levels of physical activity and diet were assessed by dual-energy X-ray densitometry, physical activity questionnaire and 3-day food diary, respectively. Among the overweight participants, we found that: (i) groups with sleep disorders had higher fat mass in trunk and android regions than the group without sleep disorder ($P = 0.048$–$0.004$); (ii) the insomnia-only group showed a lower level of leisure-time physical activity (436.9 versus 986.5 MET min week$^{-1}$, $P = 0.009$) and higher intake of saturated fatty acids (14.8 versus 12.7 E%, $P = 0.011$) than the group without sleep disorder; and (iii) the comorbid group had a lower level of leisure-time physical activity (344.4 versus 986.5 MET min week$^{-1}$, $P = 0.007$) and lower folate intake (118.9 versus 152.1 μg, $P = 0.002$) than the group without sleep disorder, which were independent of body mass index. The results suggest that central obesity is associated with insomnia and/or obstructive sleep apnea. In addition, low levels of leisure-time physical activity and poor dietary intakes are related to insomnia or comorbid insomnia and obstructive sleep apnea among overweight men.

## INTRODUCTION

Sleep disorders such as insomnia and obstructive sleep apnea (OSA) have become a significant health issue worldwide. The prevalence of insomnia has been estimated as 6–7% among the US and European populations (Ohayon, 2002; Wittchen *et al.*, 2011), while more than 30% of the population may suffer at least one symptom related to insomnia (Ohayon, 2002). In Finland, the prevalence of diagnosed insomnia is 11.7%, which is 1.5–2 times higher than other European countries (Ohayon and Partinen, 2002). OSA is another sleep disorder with increasing prevalence, which affects 3–17% American adults in different age and gender groups, and is most observed commonly among men from middle to old age (Peppard *et al.*, 2013). The prevalence of OSA is approximately 8% among Finnish population (Kronholm *et al.*, 2009). Insomnia and OSA also often exist as comorbidity (Luyster *et al.*, 2010).

An increasing number of studies have shown the association between obesity and sleep disorders. One study

 

suggests that obese individuals are 50% more likely to suffer insomnia than participants of normal weight, thus obesity is regarded as a risk factor for insomnia (Singareddy *et al.*, 2012). The association between obesity and OSA is more widely recognized (Punjabi, 2008). More than two-thirds of individuals with OSA are obese (Punjabi, 2008; Vgontzas *et al.*, 2000), and 25% of overweight adults with body mass index (BMI) of between 25 and 28 have at least mild OSA (Romero-Corral *et al.*, 2010). In addition, the link between fat distribution and OSA severity has been noted; there is an association between abdominal fat volume and apnea–hypopnea index (AHI) (Pillar and Shehadeh, 2008; Schäfer *et al.*, 2002). However, whether or not central obesity is associated with insomnia is unclear.

It is widely accepted that obesity is associated largely with behavioural factors, such as a low level of physical activity, poor-quality diet and an imbalance between energy intake and expenditure (Hamilton *et al.*, 2007; Swinburn *et al.*, 2004). There is accumulating evidence for a link between the above-mentioned behavioural factors and sleep disorders. A low level of physical activity is associated with both insomnia (Paparrigopoulos *et al.*, 2010) and sleep-disordered breathing (Vasquez *et al.*, 2008). However, studies regarding the relationship between patterns of physical activity and sleep disorders are scarce. The relationship between nutrition and sleep disorders also represents an important issue, but has been understudied (Partinen, 2009). In addition, alongside the high prevalence of OSA and impaired sleep quality among overweight individuals, few studies have concerned sleep disorders within the overweight population. We assumed that overweight middle-aged men with insomnia and/or OSA had higher fat mass in the central body area, a lower level of physical activity and poorer diet, compared to normal or overweight middle-aged men without sleep disorder.

## METHODS

### Participants

This is an exploratory ancillary study, based on the baseline data of a randomized controlled lifestyle intervention trial for middle-aged men with sleep disorders (the MOTOSD study, ISRCTN77172005) (Tan *et al.*, 2013). Participants for this study comprised a total of 211 Finnish men aged 30–65 years who resided in the city of Jyväskylä and its surroundings with a population of 150 000 inhabitants. They were recruited voluntarily. The recruitment process is shown in Fig. 1.

There were five study groups. (i) Participants with insomnia first reported insomnia complaints through local public health care centres, the outpatient clinic of the local hospital or through advertising on radio news media and the internet. They were then invited to answer a sleep disorder screening questionnaire [the Vitalmed sleep questionnaire, which included all the questions in the Basic Nordic Sleep Questionnaire (Partinen and Gislason, 1995) and the Epworth Sleepiness Scale (ESS) (Johns, 1991)]. On the basis of their answers, insomnia was classified if the predominant complaints were difficulty in initiating and/or maintaining sleep and/or non-restorative sleep, and the sleep complaints had lasted for at least 1 month during the last 3 months (APA, 2000). (ii) Participants with OSA were recruited from the outpatient pool of the Central Finland Health Care District. OSA patients who had relevant medical history during the past 2 years with 5≤AHI<30 were invited. OSA was diagnosed by a physician specialized in respiratory diseases and sleep medicine, according to one overnight home-based ambulatory Level III polysomnography (PSG) test (Embletta; Embla Systems, Amsterdam, the Netherlands) and the Vitalmed sleep questionnaire. The diagnoses were based on the following criteria: an AHI of 5 or greater with excessive daytime sleepiness or an AHI of 15 or greater, regardless of associated symptoms (American Academy of Sleep Medicine Task Force, 1999). Excessive daytime sleepiness was assessed by ESS in the Vitalmed Sleep Questionnaire; participants with 5≤AHI<15 and an ESS score of more than 10 were included. The average AHI of the 35 participants diagnosed with OSA was 20.6 [95% confidence interval (CI): 14.3–26.9]. Thirteen participants were undertaking continuous positive airway pressure (CPAP) treatment by the time of recruitment. (iii) The comorbid insomnia and OSA groups were combined in two parts. First, participants with

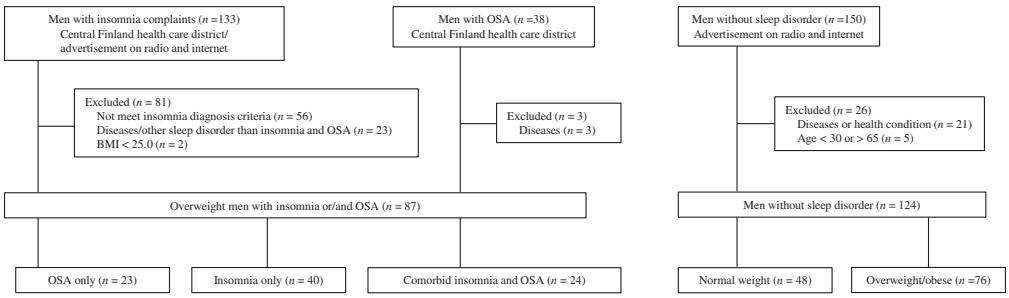


**Figure 1.** Flow Diagram of Study Enrollment.

diagnosed OSA who also fulfilled the insomnia diagnosis criteria by sleep disorders screening questionnaire ($n = 6$) were included. Then, participants with insomnia who fulfilled suspected OSA criteria of the sleep disorders screening questionnaire and had an ESS score of more than 10 ($n = 18$) were also included. The criteria for suspected OSA in the sleep disorders screening questionnaire were: snoring at least 3 nights per week, with the snores at least steady and loud; or noticed by the partner as having breath interruptions during sleep at least 1 night per week; or irregularly noticed by the partner as having breath interruptions during sleep, and sleep suspended at least twice per night; or snoring irregularly during sleep, and sleep suspended at least three times per night for at least 3 nights per week. The AHI levels of the six participants extracted from the diagnosed OSA patients did not differ significantly from the remaining patients in the OSA group. (iv, v) Participants without sleep disorders were recruited through advertising on radio news media and the internet for a physical activity, diet and nutrition education programme of the MOTOSD study. They did not have any reported long-term (more than 1 month) sleep complaint, nor did they have any diagnosed sleep disorder, according to their medical history.

Medical and family health histories of all participants were examined by a physician. Participants with major psychiatric illnesses, alcoholism, diabetes mellitus, Crohn's disease, sarcoidosis, coeliac disease, thyroid, liver and severe heart diseases, chronic diarrhoea, ulcerative colitis, rheumatoid arthritis, severe osteoarthritis, systemic lupus erythematosus, cancer, chronic pain conditions, other sleep disorder than insomnia and OSA and current or regular use of sedatives, hypnotics and painkillers were excluded.

Finally, among 163 overweight or obese [body mass index (BMI) = 25.0–42.9] participants, there were 23 OSA only, 40 insomnia only (INS), 24 comorbid insomnia and OSA (COM) and 76 free from any sleep disorder (HOW). The remaining 48 participants had normal weight (BMI = 21.0–24.9) without any diagnosed sleep disorder (HNW). Informed consent was obtained from all participants prior to the study. The study was approved by the Ethics Committee of the Health Care District of Central Finland.

## Measurements

### *Background information and anthropometric measurements*

Age, education, smoking habits and self-rated health status were obtained through the health history questionnaire. All anthropometric measurements were performed after overnight fasting (12 h). Height was measured using a fixed wall-scale device to the nearest 0.1 cm. Weight was determined to the nearest 0.1 kg using an electronic scale, calibrated before each measurement session. BMI was calculated as weight (kg) per height$^2$ (m$^2$). Chest, waist, hip and neck circumferences were determined using a measuring tape in the conventional manner to the nearest 0.1 cm.

### *Fat mass assessment*

Fat mass of the whole body and different body sections (arm, trunk, leg, android and gynoid) were assessed by using dual-energy X-ray densitometry (DXA; Prodigy, GE Lunar, Madison, WI, USA). Validation studies of DXA against computed tomography have shown high reliability of the method in assessing abdominal fat mass ($n = 75$, $R = 0.97$) (Glickman *et al.*, 2004) and leg fat mass ($n = 18$ and 34, $R = 0.93$ and 0.94) (Bredella *et al.*, 2010). Body fat percentage was calculated based on fat mass (kg) per total body weight (kg).

### *Physical activity assessment*

A self-administrated physical activity questionnaire was used to evaluate levels of physical activities. The questionnaire recorded the participant's physical activity level during leisure time, commuting and household tasks. Working duration per workday was also recorded. For instance, leisure-time physical activity (LTPA) included outdoor and indoor physical exercise and other physically active leisure-time tasks, such as yard work, but indoor household tasks such as cleaning and cooking were not included. Considering the drastic climatic differences between seasons in the study region, which might affect the choice of exercise activity and means of transportation, LTPA and commuting physical activity information was solicited separately for the summer (April–September) and winter (October–March) half-years. For each half-year, the questionnaire asked for the two types of most frequently performed LTPA, together with the duration of each session and the number of sessions each week. Means of commuting were listed as walking, cycling, driving a car or another mode of transport, each followed by time duration per workday. For household tasks, total time duration per week was requested.

The amount of physical activity was then determined by metabolic equivalent (MET) multiplied by time duration in min per week (MET min week$^{-1}$]. One MET is approximately 3.5 mL oxygen consumption per kg body weight per min, or 1 kcal energy consumption per kg body weight per hour (Ainsworth *et al.*, 2011). METs of all events recorded in LTPA, commuting physical activity and household tasks were referenced to the 2011 Compendium of Physical Activities (Ainsworth *et al.*, 2011). For activities with a wide range of activity intensity or for which the intensity level could not be determined, the METs of the general or moderate level were applied. Physical activity levels for the different types of physical activity were calculated as:

$$\text{LTPA level}\,(\text{MET min week}^{-1}) = \Big[\sum\nolimits_{S1-S2}(\text{MET} \times \text{duration} \times \text{frequency}) + \sum\nolimits_{W1-W2}(\text{MET} \times \text{duration} \times \text{frequency})\Big]/2$$

where $S_1$–$S_2$ = the two LTPA events in summer half-year, $W_1$–$W_2$ = the two LTPA events in the winter half-year,

duration = min per session and frequency = times per week.

$$\text{Commuting physical activity level (MET min week}^{-1}) = \left[\sum_{S1-Sn}(\text{MET} \times \text{duration} \times \text{frequency}) + \sum_{W1-Wn}(\text{MET} \times \text{duration} \times \text{frequency})\right]/2$$

where $S_1$–Sn = the ways of commuting in the summer half-year, $W_1$–Wn = the ways of commuting in the winter half-year, duration = min per workday and frequency = number of workdays per week.

$$\text{Household physical activity level (MET min week}^{-1}) = \text{MET} \times \text{duration}$$

where MET = 3.5 and duration = total min of household physical activities per week (Ainsworth *et al.*, 2011).

Physical activity level assessed by the questionnaire had been validated against activity energy expenditure estimated through doubly labelled water and indirect calorimetry ($n$ = 17, $R$ = 0.651) (Völgyi *et al.*, 2011). In addition, physical inactivity information was obtained from the physical activity questionnaire, which involved recording total sedentary (sitting) hours per day, sedentary hours in work per workday and total lying down hours per day.

### *Dietary intake assessment*

All food consumption data were analysed from a 3-day food diary and detailed information was reported elsewhere (Tan *et al.*, 2013). Briefly, a food diary was kept for a period including 2 working days and 1 weekend day. The diary included the name and estimated amount of all food and drink consumed during each day. The Micro-Nutrica PC program was used to estimate the nutrient intakes, as well as the proportions in total energy intake of energy-yielding nutrients (E%) (Rastas *et al.*, 1997). The Nutrica database of foodstuffs and their nutrient content have been updated with new products and brand names used by the participants. Data of non-energy yielding nutrients are shown after adjustment to a standard 1000 kcal energy intake, in order to eliminate the influence of differences in total consumption between individuals.

## Statistical analysis

IBM SPSS statistics version 22 (SPSS, Inc., Chicago, IL, USA) was used to perform statistical analysis. All data were checked for normality by Shapiro–Wilk's $W$-test and for homogeneity by Levene's test before each analysis. Natural logarithm transformations were performed on non-normally distributed data. One-way analysis of variance (ANOVA) followed by Sidak multiple comparison tests were used to estimate the between-group differences of continuous variables. The generalized estimating equation was used to estimate the between-group differences of categorical variables. In addition, one-way analysis of covariance (ANCOVA) adjusted for BMI, and BMI, age, education level and smoking habit were carried out on selected continuous variables, respectively. Pairwise differences were checked further by Sidak multiple comparison tests. A $P$-value <0.05 was set as significant in all tests.

## RESULTS

General characteristics of study participants are shown in Table 1. There were no significant differences in age and height between the groups. The HNW group differed significantly in most of the anthropometric and body compositional outcomes from other groups. Compared to HOW, all groups with sleep disorder showed higher chest and waist circumferences, fat mass of trunk and android regions ($P$ = 0.048 to <0.001); groups with OSA showed higher weight and BMI ($P \leq 0.001$); COM also showed higher fat mass ($P$ = 0.039). No difference in fat mass percentage was found among the HOW and sleep-disordered groups. The HNW group had a higher tertiary education rate than the HOW and COM groups ($P$ = 0.012 and 0.030, respectively) and lower smoking rate than the HOW and INS groups ($P$ = 0.031 and 0.015, respectively). Moreover, self-rated health condition differed significantly among HNW, HOW and groups with sleep disorder ($P$ = 0.013 to <0.001). More than 70% of the HNW participants considered their health status as 'good'; however, the rate was gradually lowered through the HOW, OSA and INS groups, and showed the lowest rate as 0% in the COM group. On the contrary, more than half the participants in the COM group considered their health status as 'poor', while among the HNW group this rate was 6.3%.

Table 2 shows the levels of physical activity among the study groups. The HNW group had a significantly higher level of LTPA compared to the INS and COM groups (both $P < 0.001$), but not to the HOW and OSA groups. HOW also had a higher LTPA level than the INS and COM groups ($P$ = 0.003 and 0.001, respectively), but not than the OSA group. No between-group difference was found among levels of commute physical activities and household physical activities, as well as daily sedentary time, lying down time and work time durations.

Proportions of energy-yielding nutrients (E%) in total energy intake are shown in Table 3. All groups with sleep disorder had a lower E% of carbohydrates than HNW ($P$ = 0.012 to <0.001); INS also had a lower carbohydrate E% than HOW ($P$ = 0.008). Compared to HNW and HOW, a higher E% of total fat was found in INS ($P$ = 0.001 and 0.003, respectively), and a higher E% of saturated fatty acids (SFA) was found in both the INS and COM groups ($P$ = 0.028–0.007). The E% of protein did not differ among the groups.

**Table 1** Descriptive statistics by study groups

| | *HNW* (n = *48*) *Mean (SD)* | *HOW* (n = *76*) *Mean (SD)* | *OSA* (n = *23*) *Mean (SD)* | *INS* (n = *40*) *Mean (SD)* | *COM* (N = *24*) *Mean (SD)* |
|---|---|---|---|---|---|
| Age (years) | 50.9 (6.8) | 50.4 (7.0) | 52.5 (8.0) | 49.4 (10.0) | 51.3 (9.2) |
| Height (cm) | 178.5 (6.1) | 177.3 (6.0) | 179.8 (7.1) | 179.4 (5.9) | 178.0 (4.5) |
| Weight (kg) | 74.5 (5.7) | 88.5 (9.1)[a] | 100.4 (14.8)[a,b] | 94.0 (11.6)[a] | 99.2 (16.2)[a,b] |
| BMI | 23.4 (1.1) | 28.2 (2.6)[a] | 31.0 (3.9)[a,b] | 29.6 (3.5)[a] | 31.3 (5.0)[a,b] |
| Chest circumference (cm) | 96.4 (4.1) | 104.9 (6.7)[a] | 113.4 (7.6)[a,b] | 109.5 (9.2)[a,b] | 111.6 (9.0)[a,b] |
| Waist circumference (cm) | 87.4 (5.2) | 98.0 (7.6)[a] | 110.4 (9.0)[a,b] | 106.5 (10.2)[a,b] | 111.4 (14.7)[a,b] |
| Lean mass (kg) | 56.1 (4.6) | 60.3 (6.5)[a] | 66.5 (6.9)[a,b] | 63.1 (7.2)[a] | 65.0 (6.5)[a,b] |
| Fat mass (kg) | 16.1 (4.1) | 25.8 (6.2)[a] | 30.4 (9.1)[a] | 29.1 (8.6)[a] | 30.9 (10.8)[a,b] |
| Fat mass percentage (%) | 21.4 (4.1) | 28.4 (5.3)[a] | 29.7 (5.7)[a] | 30.0 (5.0)[a] | 30.4 (6.1)[a] |
| Fat mass arms (kg) | 1.5 (0.4) | 2.4 (0.7)[a] | 2.6 (0.9)[a] | 2.5 (1.0)[a] | 2.7 (1.1)[a] |
| Fat mass legs (kg) | 4.9 (1.3) | 6.9 (1.9)[a] | 7.2 (2.4)[a] | 7.2 (2.2)[a] | 7.6 (2.9)[a] |
| Fat mass trunk (kg) | 9.1 (2.8) | 15.8 (4.3)[a] | 19.7 (6.0)[a,b] | 18.5 (5.9)[a,b] | 19.7 (7.1)[a,b] |
| Fat mass android region (kg) | 1.7 (0.5) | 2.9 (0.9)[a] | 3.7 (1.1)[a,b] | 3.5 (1.2)[a,b] | 3.8 (1.4)[a,b] |
| Fat mass gynoid region (kg) | 2.8 (0.7) | 3.9 (0.9)[a] | 4.2 (1.4)[a] | 4.2 (1.2)[a] | 4.3 (1.6)[a] |
| Education (tertiary/non-tertiary, %) | 97.9/2.1 | 86.8/13.2[a] | 91.3/8.7 | 95.0/5.0 | 80.0/20.0[a] |
| Smoking (no/yes, %) | 93.8/6.2 | 81.6/18.4[a] | 82.6/17.4 | 75.0/25.0[a] | 76.0/24.0 |
| Self-rated health status (good/average/poor, %) | 70.8/22.9/6.3 | 43.4/40.8/15.8[a] | 39.1/21.7/39.1[a] | 17.5/40.0/42.5[a,b] | 0.0/48.0/52.0[a,b,c] |

HNW, healthy normal weight; HOW, overweight or obese otherwise healthy; OSA, obstructive sleep apnea; INS, insomnia; COM, comorbid insomnia and obstructive sleep apnea; SD, standard deviation.
*P*-values reflect appropriate test of significance (one-way analysis of variance followed by Sidak *post-hoc* comparison tests for continuous variables and generalized estimating equation for categorical variables).
[a]$P < 0.05$ versus HNW; [b]$P < 0.05$ versus HOW; [c]$P < 0.05$ versus OSA.

**Table 2** Outcomes of physical activity and inactivity among study groups

| | *HNW* (n = 48) *Mean (95% CI)* | *HOW* (n = 75) *Mean (95% CI)* | *OSA* (n = 23) *Mean (95% CI)* | *INS* (n = 40) *Mean (95% CI)* | *COM* (n = 24) *Mean (95% CI)* |
|---|---|---|---|---|---|
| LTPA (MET min week$^{-1}$)* | 1306.1 (1013.3, 1598.9) | 986.5 (767.6, 1205.5) | 689.5 (369.0, 1009.9) | 436.9 (280.9, 592.9)[a,b] | 344.4 (185.6, 503.1)[a,b] |
| Commute physical activities (MET min week$^{-1}$)† | 734.3 (593.8, 874.9) | 652.5 (522.5, 782.5) | 772.4 (478.2, 1066.6) | 493.3 (351.8, 634.8) | 675.5 (447.9, 903.1) |
| Household physical activities (MET min week$^{-1}$)‡ | 525.0 (427.5, 622.5) | 486.0 (402.6, 569.4) | 500.3 (358.6, 642.1) | 387.9 (277.6, 498.2) | 495.0 (345.3, 644.7) |
| Sedentary time day$^{-1}$ (h) | 7.9 (7.0, 8.9) | 7.2 (6.5, 7.9) | 8.6 (6.7, 10.5) | 8.9 (8.0, 9.8) | 7.4 (6.2, 8.6) |
| Lying down time day$^{-1}$ (h) | 8.4 (8.1, 8.7) | 8.4 (8.1, 8.7) | 8.1 (7.4, 8.9) | 8.4 (7.9, 8.8) | 8.1 (7.5, 8.6) |
| Work time working day$^{-1}$ (h) | 8.3 (8.0, 8.6) | 8.4 (8.1, 8.7) | 8.3 (7.8, 8.9) | 8.5 (8.2, 8.9) | 8.8 (8.3, 9.3) |

HNW, healthy normal weight; HOW, overweight or obese otherwise healthy; OSA, obstructive sleep apnea; INS, insomnia; COM, comorbid insomnia and OSA; LTPA, leisure-time physical activity; MET, metabolic equivalent; CI, confidence interval.
*P*-values reflect significance tested by one-way analysis of variance followed by Sidak *post-hoc* comparisons tests.
[a] $P < 0.05$ versus HNW; [b] $P < 0.05$ versus HOW.
*P-values for natural log-transformed results.
†HNW = 42; HOW = 59; OSA = 21; INS = 34; COM = 21.
‡HNW = 46; HOW = 66; OSA = 23; INS = 36; COM = 21.

Non-energy-yielding nutrients, including dietary fibre, vitamin and mineral intakes, were also found with group differences (Table 3). There was a lower intake of dietary fibre in the INS group compared to the HNW group ($P = 0.040$). The INS and COM groups had lower intakes of thiamine than the groups without sleep disorder ($P = 0.048$–$0.002$). The COM group also had lower intakes of folate and potassium than groups without sleep disorder ($P = 0.026$–$0.002$). In addition to the above-mentioned nutrients, coffee consumption did not differ significantly between the study groups (not shown in the table).

Comparing the intake of energy-yielding nutrients to the Finnish nutrition recommendation 2014 (National Nutrition Council, 2014), we found that the sleep disorder groups were below the lower bound of the carbohydrates E% recommendation (Fig. 2). All study groups were within the recommended range for total fat, but all exceeded the recommended E% level for SFA. The protein intakes of all groups were within the recommended range. All groups but COM exceeded the recommended alcohol E% level.

After adjusting for BMI only, we found that the differences between the COM and HOW groups remained significant in the amount of LTPA, intakes of thiamine, folate and potassium per 1000 kcal energy consumption ($P = 0.007$–$0.001$). These differences were maintained when adjusted further for BMI, age, education and smoking ($P = 0.009$ to $<0.001$). However, the difference in SFA E% between the two groups was not significant after adjustment (Table 4).

## DISCUSSION

In this study we assessed whether body composition, levels of physical activities and amounts of dietary intakes were associated with insomnia and/or OSA among overweight middle-aged men. Within the overweight groups, three main findings were obtained. First, insomnia and OSA both have a strong association with central obesity. Secondly, insomnia and comorbid insomnia and OSA are associated with low levels of LTPA, but not of other types of physical activity. Moreover, dietary intakes of low carbohydrate but high SFA, plus a low intake of certain micronutrients, are linked to insomnia and/or comorbid insomnia and OSA.

It is known that obesity can affect sleep quality in general, and may predispose to OSA (Punjabi, 2008). Studies have shown that OSA-related symptoms can be alleviated through weight loss to reach normal weight levels (Romero-Corral *et al*., 2010; Tuomilehto *et al*., 2014). In addition, studies have described fat accumulation in the central or abdominal region as an important risk factor for OSA (Pillar and Shehadeh, 2008; Schäfer *et al*., 2002). It has been reported that the quantity of abdominal fat [determined by nuclear magnetic resonance imaging (MRI)] is correlated with AHI among male OSA patients (AHI>10) (Schäfer *et al*., 2002). Another study indicated that, among elderly men, central fat mass is a significant predictor of OSA in those with a severe condition (AHI>30) (Degache *et al*., 2013). We found further

**Table 3** Intakes of energy-yielding and other nutrients

| | *HNW* (n = *41*) *Mean (95% CI)* | *HOW* (n = *65*) *Mean (95% CI)* | *OSA* (n = *20*) *Mean (95% CI)* | *INS* (n = *36*) *Mean (95% CI)* | *COM* (n = *21*) *Mean (95% CI)* |
|---|---|---|---|---|---|
| Total intake per day | | | | | |
| Total energy (kcal) | 2069.8 (1945.7, 2194.0) | 2038.5 (1884.9, 2192.0) | 1893.4 (1744.5, 2042.4) | 2198.5 (2036.6, 2360.5) | 2231.7 (1957.3, 2506.2) |
| Carbohydrates (g) | 244.4 (228.8, 260.1) | 228.6 (210.6, 246.7) | 186.7 (168.2, 205.2)[a] | 216.6 (198.2, 235.1) | 224.3 (188.3, 260.4) |
| Fat (g) | 73.3 (66.9, 79.7) | 75.4 (67.9, 82.9) | 75.4 (62.9, 87.9) | 91.9 (82.7, 101.1)[a,b] | 89.7 (74.0, 105.4) |
| Protein (g) | 89.6 (83.6, 95.6) | 93.0 (86.5, 99.5) | 89.1 (78.3, 99.8) | 97.3 (88.7, 106.0) | 98.5 (85.4, 111.6) |
| Proportion in total energy intake | | | | | |
| Carbohydrates (E%) | 47.3 (45.7, 48.9) | 45.4 (43.3, 47.6) | 40.6 (36.8, 44.3)[a] | 40.2 (38.3, 42.1)[a,b] | 40.7 (36.7, 44.7)[a] |
| Sucrose (E%) | 7.6 (6.7, 8.5) | 7.1 (6.2, 8.0) | 5.1 (4.2, 6.0) | 6.6 (5.6, 7.7) | 6.5 (4.8, 8.2) |
| Total fat (E%) | 31.5 (29.6, 33.4) | 32.5 (30.9, 34.1) | 35.6 (31.7, 39.6) | 37.5 (35.7, 39.4)[a,b] | 36.1 (33.0, 39.3) |
| SFA (E%) | 12.4 (11.5, 13.4) | 12.7 (12.0, 13.5) | 14.0 (12.3, 15.6) | 14.8 (13.9, 15.7)[a,b] | 15.0 (13.7, 16.3)[a,b] |
| MUFA (E%) | 10.5 (9.8, 11.2) | 10.9 (10.3, 11.6) | 11.9 (10.0, 13.9) | 12.4 (11.5, 13.4)[a] | 11.7 (10.4, 13.0) |
| PUFA (E%) | 5.5 (4.9, 6.0) | 5.6 (5.2, 5.9) | 5.8 (4.7, 6.9) | 6.2 (5.5, 6.9) | 5.7 (4.8, 6.6) |
| Protein (E%) | 17.4 (16.5, 18.4) | 18.8 (18.0, 19.6) | 19.0 (17.3, 20.7) | 18.3 (17.0, 19.5) | 18.2 (16.5, 19.9) |
| Alcohol (E%)*[†] | 5.4 (2.5, 8.3) | 5.7 (3.7, 7.6) | 6.3 (3.5, 9.2) | 5.4 (3.9, 6.8) | 4.7 (1.7, 7.8) |
| Consumption per 1000 kcal energy intake | | | | | |
| Dietary fibre (g) | 12.8 (11.5, 14.1) | 12.2 (11.1, 13.3) | 12.3 (10.2, 14.4) | 10.1 (9.1, 11.1)[a] | 10.5 (9.1, 11.9) |
| Thiamine (mg) | 0.7 (0.7, 0.8) | 0.8 (0.7, 0.8) | 0.7 (0.6, 0.7) | 0.6 (0.6, 0.7)[a,b] | 0.6 (0.5, 0.7)[a,b] |
| Folate (μg) | 154.5 (144.8, 164.3) | 152.1 (142.5, 161.6) | 142.9 (128.4, 157.4) | 135.1 (122.6, 147.5) | 118.9 (106.7, 131.2)[a,b] |
| Vitamin C (mg) | 62.3 (51.9, 72.7) | 53.8 (46.4, 61.2) | 44.9 (32.8, 56.9) | 40.9 (32.2, 49.5)[a] | 41.4 (27.1, 55.7) |
| Potassium (mg) | 2060.9 (1908.7, 2213.1) | 2112.7(1984.8, 2240.6) | 2029.7 (1866.1, 2193.2) | 1893.3 (1771.0, 2015.6) | 1696.9 (1560.2, 1833.6)[a,b] |
| Iron (mg) | 5.9 (5.5, 6.3) | 6.2 (5.9, 6.5) | 6.3 (5.9, 6.7) | 5.8 (5.4, 6.3) | 5.3 (4.8, 5.7)[b] |

HNW, healthy normal weight; HOW, overweight or obese otherwise healthy; OSA, obstructive sleep apnea; INS, insomnia; COM, comorbid insomnia and OSA; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; CI, confidence interval.

*P*-values reflect significance tested by one-way analysis of variance followed by Sidak *post-hoc* comparison tests.

[a]$P < 0.05$ versus HNW; [b]$P < 0.05$ versus HOW.

**P*-values for the natural log-transformed results.

[†]HNW = 29; HOW = 37; OSA = 15; INS = 27; COM = 15.

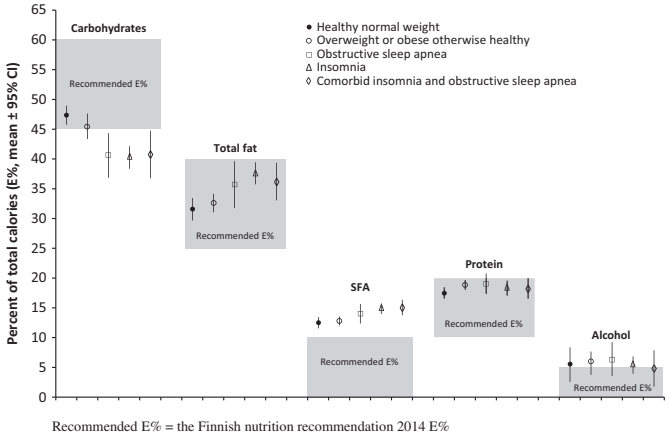


**Figure 2.** Energy-yielding nutrients and Finnish recommendations.

that although fat mass percentages were on the same level, overweight men with OSA had significantly higher central (trunk and android region) fat mass than their overweight counterparts without sleep disorder. This suggests that central obesity is worthy of notice among overweight/obese OSA patients.

The association between central body fat distribution and short sleep duration (fewer than 5 h per night, actigraphy and 5–6 h per day, habitual, respectively) has been reported in previous studies, which reflected a potential association between insufficient sleep duration and central obesity rather than total adiposity (Chaput *et al*., 2007; Patel *et al*., 2008). One study has also mentioned the role of hypothalamic–pituitary–adrenal (HPA) axis hyperactivity in both insufficient sleep and abdominal adipose (Chaput *et al*., 2011). However, whether or not their participants suffered from insomnia symptoms were not specified by the previous studies. In addition, determining fat distribution among individuals was not introduced. The results in our study showed that overweight men who suffered from insomnia and comorbid insomnia and OSA also had significantly higher fat mass accumulation in the android or trunk areas than their overweight counterparts without sleep disorder.

Physical inactivity is one of the risk factors associated with both obesity and sleep disorders (Hamilton *et al*., 2007; Sherrill *et al*., 1998). Exercise interventions exhibited treatment efficacies in prolonging sleep duration, reducing the difficulty in falling asleep (Tworoger *et al*., 2003) or lowering the AHI (Kline *et al*., 2011). It has been reported recently that higher levels of LTPA (i.e. sports), but not household physical activity, contribute to better sleep quality in middle-aged women (Kline *et al*., 2013). In our study, the groups with insomnia had significantly lower levels of LTPA than the HOW group; the disparity was independent of BMI and other covariates. However, this difference was not found between the OSA and HOW or HNW groups, which indicate that, among overweight men, mild to moderate OSA without insomnia may not be related to low levels of physical activity. Conversely, insomnia and insomnia-OSA comorbidity are associated strongly with a low level of physical activity.

The association between relatively short sleep duration (fewer than 7 h per day, habitual and fewer than 8 h per weekday, actigraphy, respectively) and high dietary fat intake has been identified previously by both across-age and age-specific studies (Shi *et al*., 2008; Weiss *et al*., 2010). However, these studies did not clarify whether or not participants had insufficient sleep duration or insomnia symptoms. The results of our study suggest that, according to the 2014 Finnish nutritional recommendation, overweight men with insomnia had a low proportion of carbohydrates in their total energy intake. A recent study based on the Japanese population also showed that low carbohydrate intake (<50% of total energy) is associated with difficulty in maintaining sleep (Tanaka *et al*., 2013). Furthermore, participants with insomnia showed a higher SFA intake than both the HOW and HNW groups. A similar result has been reported by one study, which indicated that high SFA was the primary factor behind the increased total fat intake among short sleepers (St-Onge *et al*., 2011). However, when controlling for BMI or BMI and other covariates, we found no differences in SFA intake between HOW and COM. Hence, it may also be possible that a high SFA intake among overweight men with OSA is related to obesity, but not sleep symptoms. Moreover, further studies are needed to identify if the differences in intakes of energy-yielding nutrients are due to insufficient sleep durations, or other insomnia related symptoms, or both.

All the participants in our study met the 2014 Finnish nutritional recommendation in listed micronutrients consumptions except for vitamin D, folate and iron, which were below

**Table 4** Variables differ between COM and HOW groups, before and after adjustment for covariate(s)

| | *Unadjusted* | | | *Adjusted for BMI* | | | *Adjusted for BMI, age, education level, and smoking habit* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Mean difference* | P-*value*† | *95% CI* | *Mean difference* | P-*value*‡ | *95% CI* | *Mean difference* | P-*value*‡ | *95% CI* |
| LTPA (MET min week$^{-1}$) | −642.1 | 0.001* | (−1201.7, −82.5) | −614.2 | 0.007* | (−1215.3, −13.0) | −594.6 | 0.009* | (−1198.6, 9.4) |
| SFA (E%) | 2.3 | 0.028 | (0.1, 4.4) | 1.9 | 0.145 | (−0.3, 4.0) | 2.0 | 0.101 | (−0.2, 4.2) |
| Thiamine (mg 1000 kcal$^{-1}$) | −0.2 | 0.008 | (−0.3, −0.0) | −0.2 | 0.006 | (−0.3, −0.0) | −0.2 | 0.002 | (−0.3, −0.0) |
| Folate (μg 1000 kcal$^{-1}$) | −33.1 | 0.002 | (−57.8, −8.5) | −34.3 | 0.002 | (−59.9, −8.6) | −35.8 | 0.001 | (−61.1, −10.5) |
| Potassium (mg 1000 kcal$^{-1}$) | −415.8 | 0.003 | (−731.5, −100.0) | −459.4 | 0.001 | (−786.8, −132.0) | −478.6 | <0.001 | (−804.5, −152.8) |

Data presented as the results of COM versus HOW.
SFA, saturated fatty acids; LTPA, leisure-time physical activity; MET, metabolic equivalent; BMI, body mass index; CI, confidence interval.
†*P*-values reflect significance tested by one-way analysis of variance followed by Sidak *post-hoc* comparison tests before the adjustment.
‡*P*-values reflect significance tested by analysis of covariance followed by Sidak *post-hoc* comparison tests after the adjustment.
**P*-values for natural log-transformed results.

the recommended minimum intake in each group (recommended intakes: vitamin D >5.8 μg 1000 kcal$^{-1}$, folate >189 μg 1000 kcal$^{-1}$, iron >6.7 mg 1000 kcal$^{-1}$) (National Nutrition Council, 2014). Conversely, even if the consumption of other vitamins and minerals was not deficient in terms of recommendations for basic intake, the intake differences between men with and without sleep disorder point towards potential associations between micronutrient intake and sleep. According to recent studies, lower intakes of vitamin C and potassium were associated, respectively, with non-restorative sleep and sleepiness (Grandner *et al.*, 2014) and lower serum folate concentration was related independently to sleep disturbance (Beydoun *et al.*, 2014). Similar results are also demonstrated in our study, while the underlying mechanisms remain unclear.

Our study provides some new insights in connecting physical activity-related behaviours, nutrient intake and obesity-related sleep disorders. In general, when we compared overweight men (HOW versus INS/OSA/COM), only those with insomnia or comorbid insomnia and OSA showed distinctions in LTPA amount and dietary intakes. Thus, insomnia and comorbid insomnia and OSA are associated more closely with negative behavioural factors than OSA only among overweight men, while the latter has a stronger link with obesity *per se*.

Our study has certain limitations. First, the cross-sectional analytical design does not support the detection of causality between related factors and sleep disorders, and the small sample size may reduce the strength of the findings. Secondly, many outcomes may not be regarded as predictors of sleep disorder among the general overweight and obese population, as the HOW group was free from major pathologies. Larger epidemiological studies among sleep-disordered and healthy populations are needed to further confirm the observed associations. In addition, we had no PSG data for the suspected OSA individuals in the COM group. Furthermore, the physical activity and diet outcomes were based on questionnaire and diary, which might induce reporting bias. Under-reporting is a common cause of bias in dietary surveys using food records, and underestimation of energy intake is associated with obesity in adults (Voss *et al.*, 1998). However, in our study, data of dietary intakes were entered and checked by a clinical nutritionist. To avoid the bias and possible effects of under-reporting, we adjusted the nutrients to energy intake in our analyses.

In summary, the results from our study suggest that central obesity is associated with both insomnia and OSA among overweight middle-aged men. In addition to central obesity, low levels of leisure-time physical activity and poor dietary intakes are associated with insomnia and comorbid insomnia and OSA among this population.

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## AUTHOR CONTRIBUTIONS

SC, XT, MA and TMM designed the study. XT, SMC, TMM, JT, AL, PW, AS, IT and SC carried out data acquisition. XT, MA, PW, FC, MP and SC carried out data analysis and interpretation. All authors were involved in writing the manuscript and had final approval of the submitted and published versions.

## CONFLICT OF INTEREST

No conflicts of interest declared.

## REFERENCES

Ainsworth, B. E., Haskell, W. L., Herrmann, S. D. *et al.* 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med. Sci. Sports Exerc.*, 2011, 43: 1575–1581.

American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*, 1999, 22: 667–689.

American Psychiatric Association. *Diagnostic and Statistical Manual Of Mental Disorders*, 4th edn, text revision. American Psychiatric Association, Washington, DC, 2000.

Beydoun, M. A., Gamaldo, A. A., Canas, J. A. *et al.* Serum nutritional biomarkers and their associations with sleep among US adults in recent national surveys. *PLoS One*, 2014, 9: e103490.

Bredella, M. A., Ghomi, R. H., Thomas, B. J. *et al.* Comparison of DXA and CT in the assessment of body composition in premenopausal women with obesity and anorexia nervosa. *Obesity (Silver Spring)*, 2010, 18: 2227–2233.

Chaput, J. P., Després, J. P., Bouchard, C. and Tremblay, A. Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Quebec family study. *Obesity (Silver Spring)*, 2007, 15: 253–261.

Chaput, J. P., Després, J. P., Bouchard, C. and Tremblay, A. Short sleep duration preferentially increases abdominal adiposity in adults: preliminary evidence. *Clin. Obes.*, 2011, 1: 141–146.

Degache, F., Sforza, E., Dauphinot, V. *et al.* Relation of central fat mass to obstructive sleep apnea in the elderly. *Sleep*, 2013, 36: 501–507.

Glickman, S. G., Marn, C. S., Supiano, M. A. and Dengel, D. R. Validity and reliability of dual-energy X-ray absorptiometry for the assessment of abdominal adiposity. *J. Appl. Physiol.*, 2004, 97: 509–514.

Grandner, M. A., Jackson, N., Gerstner, J. and Knutson, K. L. Sleep symptoms associated with intake of specific dietary nutrients. *J. Sleep Res.*, 2014, 23: 22–34.

Hamilton, M. T., Hamilton, D. G. and Zderic, T. W. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes*, 2007, 56: 2655–2667.

Johns, M. W. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*, 1991, 14: 540–545.

Kline, C. E., Crowley, E. P., Ewing, G. B. *et al.* The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial. *Sleep*, 2011, 34: 1631–1640.

Kline, C. E., Irish, L. A., Krafty, R. T. *et al.* Consistently high sports/exercise activity is associated with better sleep quality, continuity and depth in midlife women: the SWAN sleep study. *Sleep*, 2013, 36: 1279–1288.

Kronholm, E., Sallinen, M., Suutama, T., Sulkava, R., Era, P. and Partonen, T. Self-reported sleep duration and cognitive functioning in the general population. *J. Sleep Res.*, 2009, 18: 436–446.

Luyster, F. S., Buysse, D. J. and Strollo, P. J. Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J. Clin. Sleep Med.*, 2010, 6: 196–204.

National Nutrition Council. *Terveyttä Ruoasta—Suomalaiset Ravitsemussuositukset 2014 [The Finnish Food and Nutrition Recommendations]*. National Nutrition Council, Tampere, 2014.

Ohayon, M. M. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med. Rev.*, 2002, 6: 97–111.

Ohayon, M. M. and Partinen, M. Insomnia and global sleep dissatisfaction in Finland. *J Sleep Res.*, 2002, 11: 339–346.

Paparrigopoulos, T., Tzavara, C., Theleritis, C., Psarros, C., Soldatos, C. and Tountas, Y. Insomnia and its correlates in a representative sample of the Greek population. *BMC Public Health*, 2010, 10: 531.

Partinen, M. Nutrition and sleep. In: S. Chokoverty (Ed.) *Sleep Disorders Medicine*, 3rd edn. Elsevier, Amsterdam, 2009: 307–318.

Partinen, M. and Gislason, T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J. Sleep Res.*, 1995, 4: 150–155.

Patel, S. R., Blackwell, T., Redline, S. *et al.* The association between sleep duration and obesity in older adults. *Int. J. Obes (Lond.)*, 2008, 32: 1825–1834.

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W. and Hla, K. M. Increased prevalence of sleep-disordered breathing in adults. *Am. J. Epidemiol.*, 2013, 177: 1006–1014.

Pillar, G. and Shehadeh, N. Abdominal fat and sleep apnea: the chicken or the egg? *Diabetes Care*, 2008, 31(Suppl. 2): S303–S309.

Punjabi, N. M. The epidemiology of adult obstructive sleep apnea. *Proc. Am. Thorac. Soc.*, 2008, 5: 136–143.

Rastas, M., Seppänen, R., Knuts, L. R., Karvetti, R. L. and Varo, P. *Ruokien Ravintoainesisälto [Nutrient Composition of Foods]*. Kansaneläkelaitos, Turku, 1997.

Romero-Corral, A., Caples, S. M., Lopez-Jimenez, F. and Somers, V. K. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest*, 2010, 137: 711–719.

Schäfer, H., Pauleit, D., Sudhop, T., Gouni-Berthold, I., Ewig, S. and Berthold, H. K. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. *Chest*, 2002, 122: 829–839.

Sherrill, D. L., Kotchou, K. and Quan, S. F. Association of physical activity and human sleep disorders. *Arch. Intern. Med.*, 1998, 158: 1894–1898.

Shi, Z., McEvoy, M., Luu, J. and Attia, J. Dietary fat and sleep duration in Chinese men and women. *Int. J. Obes. (Lond.)*, 2008, 32: 1835–1840.

Singareddy, R., Vgontzas, A. N., Fernandez-Mendoza, J. *et al.* Risk factors for incident chronic insomnia: a general population prospective study. *Sleep Med.*, 2012, 13: 346–353.

St-Onge, M. P., Roberts, A. L., Chen, J. *et al.* Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. *Am. J. Clin. Nutr.*, 2011, 94: 410–416.

Swinburn, B. A., Caterson, I., Seidell, J. C. and James, W. P. Diet, nutrition and the prevention of excess weight gain and obesity. *Public Health Nutr.*, 2004, 7: 123–146.

Tan, X., Saarinen, A., Mikkola, T. M. *et al.* Effects of exercise and diet interventions on obesity-related sleep disorders in men: study protocol for a randomized controlled trial. *Trials*, 2013, 14: 235.

Tanaka, E., Yatsuya, H., Uemura, M. *et al.* Associations of protein, fat, and carbohydrate intakes with insomnia symptoms among middle-aged Japanese workers. *J. Epidemiol.*, 2013, 23: 132–138.

Tuomilehto, H., Seppä, J., Uusitupa, M. *et al.* The impact of weight reduction in the prevention of the progression of obstructive sleep apnea: an explanatory analysis of a 5-year observational follow-up trial. *Sleep Med.*, 2014, 15: 329–335.

Tworoger, S. S., Yasui, Y., Vitiello, M. V. *et al.* Effects of a yearlong moderate-intensity exercise and a stretching intervention on sleep quality in postmenopausal women. *Sleep*, 2003, 26: 830–836.

Vasquez, M. M., Goodwin, J. L., Drescher, A. A., Smith, T. W. and Quan, S. F. Associations of dietary intake and physical activity with sleep disordered breathing in the Apnea Positive Pressure Long-Term Efficacy Study (APPLES). *J. Clin. Sleep Med.*, 2008, 4: 411–418.

Vgontzas, A. N., Papanicolaou, D. A., Bixler, E. O. *et al.* Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J. Clin. Endocrinol. Metab.*, 2000, 85: 1151–1158.

Völgyi, E., Alén, M., Xu, L. *et al.* Effect of long-term leisure time physical activity on lean mass and fat mass in girls during adolescence. *J. Appl. Physiol.*, 2011, 110: 1211–1218.

Voss, S., Kroke, A., Klipstein-Grobusch, K. and Boeing, H. Is macronutrient composition of dietary intake data affected by underreporting? Results from the EPIC–Potsdam Study. European Prospective Investigation into Cancer and Nutrition. *Eur. J. Clin. Nutr.*, 1998, 52: 119–126.

Weiss, A., Xu, F., Storfer-Isser, A., Thomas, A., Ievers-Landis, C. E. and Redline, S. The association of sleep duration with adolescents' fat and carbohydrate consumption. *Sleep*, 2010, 33: 1201–1209.

Wittchen, H. U., Jacobi, F., Rehm, J. *et al.* The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur. Neuropsychopharmacol.*, 2011, 21: 655–679.

# III

## Effects of aerobic exercise on home-based sleep among overweight and obese men with chronic insomnia symptoms: a randomized controlled trial

by

Tan X, Alén M, Wiklund P, Partinen M, Cheng S

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# IV

## Six-month weight-controlling diet intervention improves sleep among overweight and obese men with chronic insomnia symptoms: a randomized-controlled trial

by

Tan X, Alén M, Wang K, Tenhunen J, Wiklund P, Partinen M, Cheng S

Submitted for publication.