Obstructive sleep apnea in severely obese subjects
Diagnosis, association with glucose intolerance and the effect of surgical and non-surgical weight loss

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CONTENTS

ACKNOWLEDGEMENTS 5
ABBREVIATIONS 7
LIST OF PAPERS 9

1 INTRODUCTION 10

1.1 History of sleep registration and obstructive sleep apnea 10
1.2 Obstructive sleep apnea 11
1.2.1 Definition 11
1.2.2 Diagnosis of obstructive sleep apnea 12
1.2.3 Symptoms of obstructive sleep apnea 13
1.2.4 Increasing prevalence of obstructive sleep apnea in the general population 14
1.2.5 Risk factors of obstructive sleep apnea 15
1.2.6 Consequences and complications of obstructive sleep apnea 16
1.2.7 Obstructive sleep apnea and glucose intolerance 17

1.3 Obesity 18
1.3.1 Definition of obesity 19
1.3.2 Obesity prevalence trends 19
1.3.3 Obesity and obstructive sleep apnea 19
1.3.4 Other complications of obesity 21

1.4 Treatment 21
1.4.1 Treatment of obstructive sleep apnea 21
1.4.2 Treatment of obesity 22

1.5 Summary of introduction 25

2 AIMS OF THE THESIS 27

3 MATERIALS AND METHODS 28

3.1 Overview of study designs 28
3.2 Participants and study design

3.2.1 Non-randomized clinical trial including cross sectional analysis of baseline data (Paper I and II)

3.2.2 Validation study (Paper III)

3.3 Clinical characteristics and definitions

3.4 Sleep registration, device descriptions and definitions

3.4.1 Embletta™

3.4.2 ApneaLink™

3.5 Laboratory analyses (paper I)

3.6 Statistics

3.7 Ethics

3.7.1 Approvals

3.7.2 Funding

4 SUMMARY OF RESULTS

4.1 Paper I

4.2 Paper II

4.3 Paper III

5 DISCUSSION

5.1 Methodological considerations

5.1.1 Study designs and statistics

5.1.2 Sleep registration and diagnostic criteria

5.1.3 Epworth Sleepiness Scale

5.2 General discussion on specific findings

5.2.1 Obstructive sleep apnea and glucose intolerance

5.2.2 Obstructive sleep apnea and weight reduction

5.2.3 Obstructive sleep apnea and leptin

5.2.4 ApneaLink™ as a diagnostic tool
5.3 Clinical implications 55
5.4 Topics for future research 56
6 CONCLUSIONS 57
7 REFERENCES 58
8 PAPERS I-III 69
ACKNOWLEDGEMENTS

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During my time of research the single most important thing I have learned is how little I know. Just to place a tiny piece of the research puzzle in place demands loads of work. The world is not made up of blacks and whites, but of all kinds of shades and hues. The more I have learnt during these years, the less categorical my statements have become. Taking a PhD is teamwork, as all other research is, and the first person I want to thank is my supervisor Jørn Hjelmesæth. I am impressed by his pedagogic skills as well as his patience with me. Thanks also to Torbjørn Omland who willingly became my co-supervisor.

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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>AHI</td>
<td>Apnea-hypopnea index</td>
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<td>AL</td>
<td>ApneaLink</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>ASAP</td>
<td>Akershus sleep apnea project</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<td>CRP</td>
<td>c-reactive protein</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EMG</td>
<td>Electromyogram</td>
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<tr>
<td>EOG</td>
<td>Electrooculogram</td>
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<tr>
<td>ESS</td>
<td>Epworth sleepiness scale</td>
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<tr>
<td>FNE</td>
<td>First night effect</td>
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<tr>
<td>HOMA-IR</td>
<td>Homeostasis model of assessment – insulin resistance</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>hsCRP</td>
<td>High sensitive c-reactive protein</td>
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<tr>
<td>HUNT</td>
<td>Helseundersøkelsen I Nord-Trøndelag</td>
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<tr>
<td>ICSD</td>
<td>International classification of sleep disorders</td>
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<td>IDF</td>
<td>International Diabetes Federation</td>
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<tr>
<td>ILI</td>
<td>Intensive lifestyle intervention</td>
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<tr>
<td>LoA</td>
<td>Limits of agreement</td>
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<tr>
<td>MOBIL</td>
<td>Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention</td>
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<tr>
<td>MSLT</td>
<td>Multiple sleep latency test</td>
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</table>
NGT - Normal glucose tolerance

NHANE - National Health And Nutrition Examination study

ODI - Oxygen desaturation index

OR - Odds ratio

OSA - Obstructive sleep apnea

PSG - Polysomnography

REM - Rapid eye movement

ROC - Receiver operating characteristics

RYGB - Roux-en-Y gastric bypass

SBD - Sleep related breathing disorders

SD - Standard deviation

SDB - Sleep disordered breathing

SPSS - Statistical package of the social science

T2DM - Type 2 diabetes mellitus

VIF - Variance inflation factor

VPAP - Variable positive airway pressure

WHO - World Health Organization
LIST OF PAPERS


III. Fredheim JM, Røislien J, Hjelmesæth J. Validation of a portable monitor for the diagnosis of obstructive sleep apnea in morbidly obese patients. (Resubmitted to Journal of Clinical Sleep Medicine)
1 INTRODUCTION

“I remember one night at Muzdalifa, with nothing but the sky overhead I lay awake amid sleeping Muslim brothers and I learned that pilgrims from every land—every color, and class, and rank; high officials and the beggar alike—all snored in the same language”1. What this excerpt from the autobiography of Malcolm X describes is common knowledge; we all snore at one time or another. Apart from being considered a nuisance, snoring may also be a symptom of a more serious condition: obstructive sleep apnea (OSA).

1.1 History of sleep registration and obstructive sleep apnea

The fact that some people stop breathing during sleep has been known for ages. Several medical reports in particular describe OSA symptoms and severely affected patients. It is, however, only over the course of the last few decades that OSA has been recognized as a disease with potentially major complications.

The first registration of brain activity during sleep, and thereby the first sleep registration, was made by the German psychiatrist Hans Berger in 1929 2. In 1965, sleep apnea was identified by Gastaut et al. as an association between breathing abnormalities, snoring and daytime sleepiness in patients during sleep3. The disease was defined in one of the early studies of Guilleminault after a consensus meeting in 1976 4.

Prior to the introduction of microchips and computer technology there were few objective ways of measuring sleep and nocturnal breathing patterns. Accordingly, sleep medicine has evolved to be a specified medical field during the last 50 years. In 1970 the first sleep research center was established at Stanford University by William Dement. To gather more extensive information about sleep physiology a method called “polysomnography” (PSG) was introduced. In addition to the measurement of brain activity through EEG electrodes, several other measures, like respiration parameters, ECG, body position, pulse oximetry, eye movement and muscle tone were added. Current definitions of sleep apnea and EEG arousals were published by the American Academy of Sleep Medicine in 2007 5,
and provide an evolution of the classic work by Rechtschaffen and Kales\textsuperscript{6}. PSG is still the gold standard for sleep recordings, but it is expensive, complicated and requires an overnight stay in a hospital or sleep clinic. With the evolution of sleep recording equipment it is now common and widely accepted to perform unattended polysomnography with mobile recorders\textsuperscript{7}.

1.2 Obstructive sleep apnea

1.2.1 Definition

OSA is a disorder characterized by repetitive upper airway obstruction resulting in nocturnal hypoxia and sleep fragmentation. OSA is a result of an obstruction of the upper airways during sleep caused by narrow airways and inadequate motor tone of the tongue and/or airway dilator muscles.

According to the international classification of Sleep Disorders, second edition (ICSD-2), OSA is categorized as a sleep related breathing disorder (SBD)\textsuperscript{8}. All SBD’s have in common the fact that breathing problems somehow affect sleep. Other sorts of SBD, comprising of central apneas, upper airway resistance syndrome and obesity hypoventilation syndrome (fomerly “Pickwick syndrome”) are not as frequent as OSA and will not be discussed in this thesis.

Apnea-hypopnea index, or AHI, is an index used to assess the severity of sleep apnea based on the total number of complete cessations (apneas) and partial obstructions (hypopneas) of breathing occurring per hour of sleep. These pauses in breathing must last for 10 seconds or more and may be associated with a decrease in oxygenation of the blood. In general, the AHI can be used to classify the severity of disease (mild $\geq 5$ to $< 15$ events/hour, moderate $\geq 15$ to $< 30$ events/hour, and severe $\geq 30$ events/hour )\textsuperscript{5}. Although AHI may define the number of breathing cessations, it does not say how long each breathing pause lasts, nor does it reflect the number and severity of oxygen desaturations. In clinical work it is therefore important both to take note of the AHI when deciding the severity of the
disease and to take into account other factors such as the length of apneas/hypopneas, the
distribution of apneas vs hypopneas, oxygen saturation, respiratory effort related arousals
and other signs of arousals.

1.2.2 Diagnosis of OSA

Diagnosis of OSA is based on the combination of characteristic clinical features (see
subheading “Symptoms of OSA”) plus objective demonstration of abnormal breathing during
sleep. A detailed clinical assessment forms an important part of the evaluation of patients
suspected of having OSA. The gold standard for the diagnosis of OSA is polysomnography
(PSG), and provides detailed information on sleep state and respiratory and gas exchange
abnormalities in addition to a range of other variables. PSG studies generally involve a
minimum of 7 channels of recordings that include EEG, electrooculogram (EOG),
electromyogram (EMG), oronasal airflow, chest wall effort, body position, snore microphone,
ECG, and oxyhemoglobin saturation. The duration of the diagnostic study should be at least
6 hours, although this practice is not enforced in split-night studies, in which the initial part is
devoted to diagnosis but the latter part involves the initiation of CPAP therapy, at which point
an obvious case of OSA is evident. However, these studies are resource intensive in that
they generally require the facilities of a full sleep laboratory and a trained technician.

The large numbers of patients wishing to be assessed for possible OSA has focused
attention on the role of home-based sleep studies. Some of the major advantages of such
home-based studies are related to cost savings and efficacy, thereby reducing waiting lists
and reducing treatment delay. Another is that patients remain in their familiar sleep
environment. In Norway, increasing demand for sleep registrations generates long waiting
lists and considerable delays in treatment.

Sleep monitors are divided into different levels according to which channels they
utilize and whether the test is performed in-laboratory or unattended. According to the
American Academy of Sleep Medicine (formerly American Sleep Disorders Association)
studies for sleep evaluation can be classified into four levels. This classification categorizes
various types of sleep monitors according to attendance and the number of physiologic channels measured:

Level 1: Full attended in-laboratory polysomnography
        ≥ 7 channels with sleep staging

Level 2: Full unattended portable polysomnography
        ≥ 7 channels with sleep staging

Level 3: Portable, unattended sleep apnea monitors
        ≥ 4 channels, no sleep staging

Level 4: Limited unattended monitors
        1-3 channels, no sleep staging

Note: Level 3 and Level 4 devices do not measure sleep time.

1.2.3 Symptoms of OSA

Nighttime symptoms

Snoring is an important symptom of OSA given that it reflects the basic pathophysiology of the disorder. Snoring, as well as hypopneas and apneas are caused by a narrowing of the upper airways. Snoring is the most frequent symptom of OSAS, occurring in up to 95% of patients, but has poor predictive value because of the high prevalence of snoring without OSA in the general population. Concern by the bed partner about witnessed breathing pauses during sleep is a common reason for referral to a sleep clinic. Witnessed apneas is a good predictor of OSA, but says nothing about the severity. Choking or gasping during the night is another common symptom upon waking during an
obstructive apnea. Although it only lasts a few seconds it may be quite frightening for both patient and bed partner.

Insomnia, and sleep maintenance insomnia in particular, is often recognized as a symptom of OSA. There are also several other nocturnal symptoms such as nocturia, enuresis, frequent arousals, excessive sweating and impotence.

**Daytime symptoms**

Excessive daytime sleepiness is a common complaint in OSA patients and is increasingly considered to be a significant health problem which can lead to accidents, psychosocial morbidity and poor quality of life. However, the subjective evaluation of excessive daytime sleepiness is complicated by the fact that patients may complain of fatigue, tiredness and lack of energy rather than sleepiness itself. Other daytime symptoms include increased appetite, memory impairment, personality changes, irritability, morning headache, anxiety and depression.

### 1.2.4 Increasing prevalence of OSA in the general population

OSA is a common disease, which is gradually becoming more widely recognized by the general public. The extent of undiagnosed OSA in the general population has been estimated to represent 5% of adults, and at least 75% of OSA patients remain undiagnosed. In their 1988 Wisconsin Sleep Cohort Study, Young et al. demonstrated sleep apnea, as diagnosed by PSG, to be a common disorder in the general, middle aged population, affecting approximately 24% of men and 9% of women (AHI ≥ 5 events/hour). The prevalence of moderate to severe OSA (AHI ≥ 15 events/hour) was estimated to 4% in women and 9% in men. The Wisconsin project repeats PSG every 4th year, with the last article published by Peppard et al. showing the prevalence of OSA to have increased markedly over the last two decades. The current prevalence estimates of moderate to severe OSA (AHI ≥ 15 events/hour) are now 10% (95% confidence interval (CI): 7, 12) among 30–49-year-old men; 17% (95% CI: 15, 21) among 50–70-year-old men; 3% (95% CI:
2, 4) among 30–49-year-old women; and 9% (95% CI: 7, 11) among 50–70 year-old women. This shows a substantial increase in OSA over the last 2 decades (relative increases of between 14% and 55% depending on the subgroup). The main explanation of this increase is the obesity epidemic, as obesity is a risk factor for developing OSA 24.

A large Norwegian population based cohort study based on the Akershus Sleep Apnea Project (ASAP) was published in 2011 by Hrubos-Strøm et al. demonstrating a similar prevalence of sleep apnea in a middle aged (30-65 years) Norwegian population as was demonstrated in the United States some 20 years ago. The overall prevalence of OSA, AHI ≥ 5 events/hour, in the ASAP was 16% and AHI ≥ 15 events/hour 8%25. Males had a greater prevalence than females with 21% vs 13 % had an AHI ≥ 5 events/hour and 11 % vs 6 % had an AHI ≥ 15 events/hour.

1.2.5 Risk factors of OSA

The three most important risk factors for OSA are obesity, male gender and older age. Obesity is an important pathogenic factor of sleep apnea 26,27. Approximately 70% of OSA patients are obese, and obesity is the only significant risk factor that is reversible 28.

The prevalence of sleep apnea is greater in men than in women. Estimates show that the male/female ratio varies from 2:1 to 4:1 29. One explanation of the gender difference is hormonal differences resulting in different ways of storing adipose tissue, as males present with more central adiposity than females.

It is believed that the strength and activity of the pharyngeal dilator musculature decreases with aging 30. Other risk factors include menopausal status, black racial status, alcohol, sedatives and smoking.

Upper airway collapse is the key mechanism in OSA pathophysiology. This can both be due to negative pressure within the airway (as with inspiration), or to do with positive pressure outside the airways, as with local fat deposits or retrognathia. Patency is preserved by the action of the pharyngeal dilators and by the traction of the trachea. As an example,
tracheal traction decreases in central obesity, making the upper airways more susceptible to collapse.

1.2.6 Consequences and complications of OSA

OSA can cause sleep fragmentation, sympathetic activation, metabolic dysregulation, endothelial dysfunction, systemic inflammation, oxidative stress, hypercoagulation and neurohumoral changes. These changes may lead to other conditions like diabetes, hypertension, heart failure, cardiovascular disease, cerebrovascular disease and traffic accidents, which all are among the most frequent complications of OSA.

An 18 year mortality follow-up was the basis of a population-based Wisconsin Sleep Cohort sample study (n = 1522) published in 2008. They found a significant high mortality risk with untreated OSA, independent of age, sex, BMI and symptoms of sleepiness. The adjusted hazard ratio (HR, 95% CI) for all-cause mortality with severe versus no SDB was 3.8 (1.6,9.0) after excluding persons who had used CPAP treatment. The adjusted HR (95% CI) for cardiovascular mortality was 5.2 (1.4,19.2).

An observational study by Marin et al. compared the long-term cardiovascular outcomes in male OSA patients with or without CPAP treatment. 264 healthy men, 377 simple snorers, 403 people with untreated mild-moderate OSA, 235 people with untreated severe disease, and 372 people with OSA undergoing treatment with CPAP were included in the analysis. Patients with untreated severe disease had a higher incidence of fatal cardiovascular events (1.06 per 100 person-years) and non-fatal cardiovascular events (2.13 per 100 person-years) than untreated patients with mild-moderate disease (0.55, p=0.02 and 0.89, p<0.0001), simple snorers (0.34, p=0.0006 and 0.58, p<0.0001), patients treated with CPAP (0.35, p=0.0008 and 0.64, p<0.0001), and healthy participants (0.3, p=0.0012 and 0.45, p<0.0001). Multivariate analysis, adjusted for potential confounders, showed that untreated severe OSA significantly increased the risk of fatal (odds ratio 2.87, 95%CI 1.17–
and non-fatal (3.17, 1.12–7.51) cardiovascular events compared with healthy participants.

Most studies of the cardiovascular effects of OSA and CPAP use include male subjects only. A cohort study of 1116 women, median follow-up 72 months, with cardiovascular death as end-point was performed by Campos-Rodriguez et al. Women with an AHI less than 10 were the control group. Further AHI of 10 -29 events/hour was classified as mild to moderate OSA and AHI ≥ 30 events/hour as severe. Patients with OSA were classified as CPAP-treated (adherence ≥4 hours per day) or untreated (adherence <4 hours per day or not prescribed). Compared with the control group, the fully adjusted hazard ratios for cardiovascular mortality were 3.50 (CI, 1.23 to 9.98) for the untreated, severe OSA group; 0.55 (CI, 0.17 to 1.74) for the CPAP-treated, severe OSA group; 1.60 (CI, 0.52 to 4.90) for the untreated, mild to moderate OSA group; and 0.19 (CI, 0.02 to 1.67) for the CPAP-treated mild to moderate OSA group.

In conclusion, several lines of epidemiological evidence indicate that OSA is associated with increased risk of cardiovascular disease. However, although a causal relationship is biologically plausible, no randomized controlled trial has evaluated the effect of any OSA treatment on cardiovascular mortality or morbidity.

1.2.7 OSA and glucose intolerance (type 2 diabetes/prediabetes)

The association between OSA and type 2 diabetes mellitus (T2DM) is now well documented, with estimates suggesting that up to 40% of people with OSA have T2DM. Most studies have addressed the possible relationship between OSA and subsequent T2DM. A recent meta-analysis of six prospective cohort studies including a total of 5953 participants, with follow-up periods of 2.7-16 years and 332 incident cases of T2DM, showed that moderate to severe OSA was associated with a greater risk of incident T2DM (RR 1.63; 95% confidence interval (CI): 1.09-2.45) compared with the absence of OSA. Several mechanisms, including intermittent hypoxia, sleep fragmentation and immune activation may contribute to this causal pathway. During intermittent hypoxia, the
alternation between hypoxia and normoxia will resemble ischemia/perfusion events. During the hypoxic/ischemic phase, the cells adapt to a low oxygen environment. During the reoxygenation/reperfusion phase there is then a sudden increase of oxygen in the cells resulting in the production of reactive oxygen species. Increased oxidative stress is a widely accepted participant in the development and progression of T2DM and its complications.

Only a few studies have addressed the possible reverse direction of causality, that T2DM might cause OSA. Studying 941 men, West et al. showed that patients with T2DM have a high prevalence (23%) of OSA. Although a cross-sectional study, the authors speculated that T2DM might be an independent risk factor of OSA. Further, diabetic autonomic neuropathy is one factor that might partly explain the increased prevalence of OSA in patients with T2DM.

The discovery of an association between OSA and T2DM made the International Diabetes Federation (IDF) change their guidelines to implement information about OSA. At the same time, they also called for more research into the association between OSA and T2DM. Finally, few previous studies have addressed the relationship between OSA and prediabetes.

1.3 Obesity

With obesity becoming an increasing problem worldwide so too has the prevalence of OSA increased. These two highly intercorrelated conditions are both significant challenges within our time. Findings from the majority of large, long-term epidemiological studies indicate that being overweight or obese is associated with increased mortality. The lifespan of severely obese individuals is decreased by an estimated 5 to 20 years depending on gender, age and race.
1.3.1 Definition of obesity

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may impair health. The degree of obesity is often classified according to the body mass index (BMI – defined as the weight divided by the square of the height (kg/m^2)). WHO’s definition of normal weight is a BMI of 18.5-24.9 kg/m^2. Overweight is defined as a BMI ≥ 25 kg/m^2, with the subclassifications preobese (BMI 25.0 – 29.9), obese class I (30.0 – 34.9), obese class II (35.0 – 39.9) and obese class III (≥40). Morbid obesity is defined as BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with at least one obesity related comorbidity.

1.3.2 Obesity prevalence trends

Rises in BMI is a worldwide phenomenon, with there being few places where it is stable or decreasing. Between 1980 and 2008, age-standardised mean global BMI increased by 0.4–0.5 kg/m^2 per decade in men and women, with substantial differences across regions and gender. As many as 1.46 billion people worldwide were estimated to be overweight in 2008.

According to the latest report from National Health and Nutrition Examination Study (NHANES) the prevalence of obesity among US adults was 35.5% for men and 35.8% for women. The prevalence of morbid obesity was higher in women (8.2%) than in men (4.4%) Data from the HUNT study (Helseundersøkelsen I Nord-Trøndelag) demonstrates that among men, the prevalence of obesity increased from 7.7% in HUNT1 (1984-86) to 22.1% in HUNT3 (2006-8), and in women from 13.3 to 23.1%.

1.3.3 Obesity and OSA

There is a strong relationship between OSA and obesity. Approximately 70 % of patients with OSA are obese, and sleep apnea is present in 40% of obese persons. In obesity grade III (BMI ≥ 40 kg/m2) the prevalence rates of OSA are considerably higher than in the general population (often reported to be in the range of 39% to 90%) and the severity of sleep apnea is generally greater than that found in leaner clinical populations.
Peppard et al. demonstrated that a 10% change in body weight was associated with a parallel change of approximately 30% in the AHI. It is probable that OSA is worsened by obesity because of fat deposition at specific sites. Fat deposition in the tissues surrounding the upper airway appears to result in a smaller lumen and increased collapsibility of the upper airway, predisposing to apnea. Central obesity (large neck circumference and visceral obesity) increases the pressure on upper airways and reduces the tension and hence the compliance of the trachea, which again makes the obese patient more susceptible to OSA. The causal relationship between OSA and obesity is probably bidirectional. There is compelling evidence demonstrating that obesity predisposes a person to OSA and that losing weight results in OSA improvement, although some studies also suggest that OSA itself may cause weight gain. Newly diagnosed OSA subjects have difficulty losing weight and may be predisposed to excessive weight gain compared to similarly obese subjects free of OSA. Factors such as reduced activity levels and increased appetite may contribute to weight gain in OSA patients.

The repeated nocturnal activation of the sympathetic nervous system associated with OSA might contribute to obesity through inhibition of leptin secretion. Leptin is primarily produced by adipocytes and its level in the blood is proportional to fat mass. Leptin suppresses appetite and affects energy expenditure. On the other hand, Ghrelin, which is primarily secreted by the stomach, conveys an appetite stimulating message to the hypothalamus. Others have demonstrated that OSA is associated with leptin resistance and high levels of both leptin and ghrelin, and short sleep duration is thought to be the main contributing factor. OSA is also associated with elevated levels of c-reactive protein (CRP) and pro-inflammatory cytokines. CRP has been identified as one of the major serum leptin-interacting proteins, and may be one of the main agents responsible for leptin resistance in OSA. OSA also stimulates the hypothalamic–pituitary–adrenal axis, resulting in excessive cortisol secretion. Exposure to excessive cortisol leads to weight gain, insulin resistance and metabolic syndrome.
1.3.4 Other complications of obesity

Obesity has several serious health effects and is associated with both increased morbidity and mortality\(^87,88\). Quality of life is also impaired in both OSA and obesity\(^89\). Obesity is associated with several life-threatening complications and contributes to ischaemic heart disease, stroke and diseases linked to the metabolic syndrome, such as hypertension, the dyslipidaemias, nonalcoholic steatohepatitis and polycystic ovary syndrome\(^90\). The risk for developing cancer is also increased, particularly for colorectal cancer, but also oesophageal, pancreatic, renal, endometrial, breast and gall bladder cancers\(^91,92\). Other obesity related complaints such as back pain, degenerative diseases of the hips and knees and depression are common\(^93\). Data from the 2010 Global Burden of Disease study show that the most prevalent risk factor for years of life lost in Norway is dietary risks (and as a consequence obesity), with smoking being in second place\(^94\).

1.4 Treatment

1.4.1 Treatment of OSA

As OSA treatment now has become readily available it is important to diagnose affected patients in order to relieve symptoms and prevent complications\(^38\). The management of OSA was revolutionized with the introduction of continuous positive airway pressure (CPAP), first described in 1981 by Colin Sullivan and associates in Sidney, Australia\(^95\). As the machines became more user friendly, smaller and less noisy, CPAP was widely adopted by the end of the 1980s. Previously, the ultimate treatment for OSA was tracheostomy, which bypassed anatomical areas susceptible to collapse in the upper airways. Although an effective treatment form, tracheostomy is invasive and not without complications.

Mandibular advancement devices are another treatment option for selected patients, and the effect has been well documented in mild and moderate OSA\(^96\). Different kinds of
surgery are recommended in different patients, despite the fact that the long term effect is controversial \(^97\). Lifestyle changes with a focus on exercise, healthy diet and weight reduction are often recommended as a part of OSA treatment and as a complement to other treatments which prevent deterioration of the condition\(^{98,99}\).

Despite the close relationship between OSA and obesity, only a few published randomized controlled trials have assessed the effect of weight loss on OSA \(^{100-102}\). Tuomilehto et al examined the effect of a very low calorie diet followed by lifestyle counseling for one year in overweight and obese patients with mild OSA\(^{100}\). The intervention group had a significantly lower odds of having OSA at follow-up than the control group; OR 0.24 (95% CI 0.08, 0.72). In the Sleep AHEAD study intensive lifestyle changes in overweight or obese patients with T2DM and mild to severe OSA were associated with a significant improvement in AHI \(^{101}\). Finally, Johansson et al reported that a nine week very low energy diet in obese men with moderate to severe OSA improved OSA (particularly severe OSA) compared to a control group which adhered to their usual diet\(^{102}\).

A meta-analysis performed by Ashrafian et al aimed to determine whether there was a greater AHI reduction in surgical compared to non-surgical weight loss studies\(^{103}\). However, because of the heterogeneity and quality of the available trials, the authors were unable to conclude whether there was a relative benefit on AHI from surgical methods or not.

According to the available evidence weight reduction reduces AHI, but it is unknown how lifestyle modifications and bariatric surgery differ in terms of their ability to reduce OSA.

1.4.2 Treatment of obesity

To reduce weight there are two main principles that form the basis of all treatment; to reduce energy intake and to increase energy expenditure. A medical approach to achieving weight loss includes dietary modifications, physical activity, drugs and behavioural interventions. The surgical approach includes different types of bariatric surgery. As with
medical treatment, the long term (≥ 1 year) weight reduction is expected to be 5-20%, in contrast to surgical treatment which has a long term weight loss of around 30% ⁱ⁰⁴-ⁱ⁰⁶.

The cornerstones of obesity treatment are diet, exercise and behavior therapy; together referred to as lifestyle modification. Lifestyle modification is different from dieting, with dieting implying adherence to a particular programme for a set period of time. Lifestyle modifications, however, may be sustained over an entire life span if desired. The maintenance of weight reduction, regardless of the initial method of reducing weight, relies on lifelong lifestyle modifications. Bariatric surgery is basically an extreme means of helping patients to change their eating behavior. If the patients return to their old eating habits after bariatric surgery then they will regain weight.

**Dietary interventions**

Dietary interventions for obesity are designed to motivate the patient to consume fewer calories than he or she expends (a negative energy balance). Energy requirements vary by sex, weight and level of physical activity. The greater the energy deficit is the greater is the weight loss. According to the National Institute of Health’s 2000 publication “Practical Guide to the Identification, Evaluation and Treatment of Overweight and Obesity in Adults”, calorie restricted diets designed to create an energy deficit of 500-1000kcal/day may induce a weight loss of 0.5-1 kg during the first weeks ¹⁰⁷, and 10-20 kg during the first year ¹⁰⁸. If a larger weight loss is necessary, a low-calorie diet (LCD; 800-1200 kcal/day) or a very-low-calorie diet (VLCD; < 800 kcal/day) may be appropriate for 3-12 weeks ¹⁰⁹. ¹⁰⁷

**Physical activity**

The benefits of physical activity include inducing calorie expenditure, sparing fat-free mass during weight loss and improving cardiovascular fitness. The greatest benefit of physical activity is that it facilitates the maintenance of weight loss ¹¹⁰. Subjects who receive
diet plus exercise maintain greater weight losses 1 year after treatment than those who diet only \textsuperscript{111}.

Isolated physical activity without weight loss may also have a positive effect on OSA \textsuperscript{112}. Exercise leads to more muscles and less fat; the lower pharyngeal pressure from diminished fat deposits might decrease the severity of OSA.

**Behavior therapy**

Behavior therapy provides patients a set of principles and techniques to facilitate their adherence to the diet and activity goals described above. Common techniques include self-monitoring (of food and activity), stimulus control, slow eating, cognitive restructuring, problem solving and relapse prevention \textsuperscript{113}.

**Surgical Interventions**

Bariatric surgery, the most intensive treatment for obesity, is appropriate for morbidly obese individuals who have failed to lose weight by other means \textsuperscript{114}. Several studies have also indicated that bariatric surgery is effective in the treatment of T2DM \textsuperscript{115-117}, although the supporting evidence is debatable \textsuperscript{118}. The number of bariatric surgery procedures have increased during the last decade in tandem with the increasing prevalence of obesity \textsuperscript{119}. Surgical intervention utilizes two different approaches to weight loss: reducing food intake by restricting gastric volume and malabsorbtive procedures, which reduce energy uptake by bypassing parts of the gastrointestinal tract. These two principals may be combined in the same surgical procedure. The first procedures were carried out in the 1950’s and they were purely malabsorptive. Serious complications mean that this procedure gave way to restrictive methods in the 1980’s and 90’s, again with their set of complications.
The gastric bypass procedure, combining malabsorption and restriction, is now the most common procedure in bariatric surgery. The procedure has been modified since its introduction in the 1960’s to its present form today \(^\text{120}\). This is by far the most common bariatric procedure performed in Norway today and accounts for more than 90 \% of all procedures \(^\text{121}\). A Roux-en-Y gastric bypass first divides the stomach into a small upper pouch of about 30 ml and a much larger, lower “remnant” pouch. The small pouch is then anastomosed to a Roux-en-Y proximal jejunal segment (Figure 1).

![Figure 1. Roux-en-Y gastric bypass (Figure by K.Toverud \(^\text{122}\)).](image)

### 1.5 Summary of introduction

Although the symptoms of OSA have been known for centuries, research on the illness spans only a few decades. The gold standard for diagnosing OSA is PSG, but with increasing prevalence in the general population there is a growing demand for more simplified and efficient methods of diagnosis. Several lines of evidence suggest that weight reduction in obese subjects reduces AHI, but the comparative effectiveness of intensive
lifestyle modification and bariatric surgery on the severity of OSA has not previously received attention. Finally, the association between OSA and T2DM is well documented, but the odds of OSA among severely obese subjects with prediabetes or T2DM compared to those with normal glucose tolerance has not been explored.
2 AIMS OF THE THESIS

The specific aims of the studies in this thesis were

1. to investigate whether treatment seeking grade III obese patients with type 2 diabetes or prediabetes have higher odds of obstructive sleep apnea than their counterparts with normal glucose tolerance.

2. to assess whether Roux-en-Y gastric bypass would be more effective than intensive lifestyle intervention at reducing the prevalence and severity of obstructive sleep apnea in morbidly obese patients.

3. to validate the diagnostic accuracy of a simple three channel (type IV monitor) sleep registration device (ApneaLink™) in a population of treatment seeking morbidly obese patients.
3 MATERIALS AND METHODS

3.1 Overview of study designs

The results in this thesis are based on cross sectional (paper I) and longitudinal data (paper II) from the one-year non-randomized controlled clinical MOBIL study (Morbid Obesity treatment, Bariatric versus Intensive Lifestyle intervention) and data from the validation study of the ApneaLink™ (paper III).

Table 1 Study design, population and sample size

<table>
<thead>
<tr>
<th>Paper</th>
<th>Study design</th>
<th>Population</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cross sectional study</td>
<td>Treatment seeking subjects with obesity grade III</td>
<td>137</td>
</tr>
<tr>
<td>II</td>
<td>Non-randomized controlled study</td>
<td>Treatment seeking morbidly obese subjects</td>
<td>59 Intensive Lifestyle Interv</td>
</tr>
<tr>
<td>III</td>
<td>Validation study</td>
<td>Treatment seeking morbidly obese subjects</td>
<td>105</td>
</tr>
</tbody>
</table>

3.2 Participants and study design

Participants in all three studies were referred to the Morbid Obesity Centre at Vestfold Hospital Trust, a regional tertiary care center in Health Region South East, Norway. The center is located in Tønsberg and serves around 1 million inhabitants in Southern Norway. It was established in 2004 and is today one of two tertiary health care centers treating morbidly obese in South-Eastern Norway. The main tasks of the center are to evaluate, assess and treat morbidly obese subjects, to conduct research in the field and to educate and support other health care centers treating obese patients 123. The intensive lifestyle intervention programme was carried out at Evjeklinikken, a center specializing in obesity treatment. The
participants in paper I had obesity grade III (BMI ≥ 40 kg/m²) and the participants in the two other papers were all morbidly obese.

3.2.1 Non-randomized clinical trial including cross sectional analysis of baseline data (Paper I and II)

Papers I and II include treatment seeking morbidly patients who participated in the MOBIL study. A flowchart of the patients in the MOBIL study is presented in figure 2. The study aimed to compare the effects of bariatric surgery and intensive lifestyle intervention on various obesity related comorbidities. The sample size (80 % statistical power, α-level of 0.05 and equal distribution to the treatment groups) was calculated based on anticipated remission rates of OSA and T2DM. Given remission rates of OSA of 30 % in the surgery group and 10 % in the ILI group, at least 65 subjects with OSA were required.

Patients (n=228) were pre-screened for participation in the study between December 2005 and May 2006. The 181 patients who satisfied the criteria for bariatric surgery and wanted either gastric bypass surgery or intensive lifestyle intervention were referred to a screening examination. This baseline examination included sleep registration, an oral glucose tolerance test, 24-hour ambulatory blood pressure monitoring, pulmonary function tests, quality of life questionnaires and a structured dietary interview. A total of 146 patients were enrolled in the study with 66 patients in the intensive lifestyle intervention group and 80 patients in the surgery group. The decision as to which treatment option to choose was based on a thorough assessment made by the multidisciplinary team (internist, dietitian, nurse, physiotherapist and surgeon). During the first visit the internist established a detailed medical history, checked previous diagnostic workups, performed a physical examination and briefly informed the patients of further investigations and treatment alternatives. At the second visit the doctor reiterated this message, providing complete information about the possible risks and benefits of an operation and encouraging the patients to incorporate their own values and preferences in the decision-making process. If no contraindication against
surgery existed, the patient and the physician together agreed upon the most appropriate choice of therapy; either surgical or conservative\textsuperscript{129}.

Patients in the surgical group completed a low calorie diet (800-900 kcal/day) three to six weeks prior to surgery with Roux-en-Y gastric bypass in order to reduce liver size. They were all encouraged to normalise eating behaviour and increase their physical activity.

Patients in the intensive lifestyle intervention group were all referred to a rehabilitation center specializing in treating morbidly obese. All but four patients were at a center called Evjeklinikken, whilst the remaining patients stayed at places with similar programmes. The programme included four stays at the center (1 week at center, 10 w home, 4 w center, 12 w home, 1 w center, 23 w home, 1 w center). The programme included organized physical activity (3–4 h), psychosocially oriented interventions and individual consultations with a medical doctor, nutritionist, physiotherapist and trained nurse. Those leading the counseling interviews were trained in motivational interviewing, a client-centered counseling style that aims to invoke behavioral changes. The patients also took part in group sessions focusing on the emotional aspects of sedentary behavior and classroom lessons on topics related to nutrition, physical activity and co-morbidities. Patients were encouraged to follow the guidelines of the Norwegian National Council of Nutrition, which recommend that the daily intake of protein, fat, and carbohydrate, should account for 10–20%, <30%, and 50–60% of energy consumed respectively\textsuperscript{104}. When at home patients were encouraged to self-monitor their lifestyle habits (e.g. by keeping a physical activity diary and a food diary) and visit their general practitioner for weight monitoring. They were contacted by telephone every 2 weeks. The treatment aim was ≥10% weight loss. Vitamin supplements were not prescribed.

**Paper I** is based on a cross sectional analysis of baseline data from the MOBIL study, but only participants with obesity grade III (BMI≥40 kg/m\textsuperscript{2}) were included in the analysis (n=137). Since all patients in the MOBIL study were morbidly obese, patients in BMI range
35-40 kg/m² had to be excluded because they, in accordance with the definition of morbid obesity, have an obesity related comorbidity. That means there was an overrepresentation of diabetic patients in this excluded group. Of the 181 patients screened for participation in the MOBIL-study [21], 35 patients were excluded due to a BMI < 40 kg/m² (n = 32) or a missing oral glucose tolerance test (n = 3). After the exclusion of an additional nine patients who failed to comply with sleep registrations, 137 extremely obese patients (101 females) were included in the present analysis. They had a mean (SD) age of 43 (11) years and BMI of 47 (6) kg/m².

**Paper II** is based on follow-up data from the MOBIL study (1-year). All patients were morbidly obese. Of the 146 patients enrolled in the study, 66 patients were included in the intensive lifestyle intervention group and 80 patients in the surgery group. After exclusion based on different causes (see flowchart in figure 2), 59 patients completed the study in the intensive lifestyle intervention group and 74 in the surgery group. The patients in the surgery group were significantly younger and heavier than those in the lifestyle group: mean (SD) age 43 (10) versus 47 (11) years (p=0.012), and BMI 47 (6) versus 43 (5) kg/m² (p<0.001).
Figure 2. Flowchart of participants in the MOBIL study completing sleep registration.
Modified from Hofsø et al.¹⁰⁴
3.2.2 Validation study (Paper III)

Paper III is a validation study of the portable somnograph ApneaLink™ against a reference method (Embletta™). Consecutive treatment seeking morbidly obese adults were recruited between March 2009 and February 2011 from the Morbid Obesity Centre. The exclusion criteria were immobile patients and inability to equip oneself with the recording devices. A total of 114 consecutive morbidly obese patients were eligible for inclusion. After the exclusion of eight patients with BMI < 35 kg/m², 106 patients were included in the sleep study. Except for one patient with too short an evaluation time (<3 hours), all study participants successfully undertook sleep registration with Embletta™ (reference method), leaving 105 subjects, 64% (n=67) females, eligible for analysis. The patients had a mean (SD) age of 44 (11) years and BMI of 44 (6) kg/m².

3.3 Clinical characteristics and definitions

Standardised forms were used for recording demographic and clinical data. Anthropometric measures were taken with patients in an upright position wearing light clothing and no shoes. Height was measured using a wall mounted stadiometer to the nearest 0.5 cm. Weight was measured to the nearest 0.1 kg and circumferences to the nearest 1 cm. Waist circumference was measured at the midpoint between the lowest rib margin and the iliac crest. Hip circumference was measured at the level of the major trochanter and neck circumference was measured at a point just below the larynx and perpendicular to the long axis of the neck. After at least five minutes of rest, blood pressure was measured three times using a sphygmomanometer. The average of the second and third measurements was registered.

All patients apart from patients with drug-treated T2DM underwent a standardised oral glucose tolerance test ¹³⁰. The patients were categorised into three groups according to the criteria of the American Diabetes Association: NGT; fasting plasma glucose <5.6 mmol/L.
and/or 2-hour plasma glucose <7.8 mmol/L, prediabetes; fasting plasma glucose 5.6 - 6.9 mmol/L and/or 2-hour plasma glucose 7.8 - 11.0 mmol/l or T2DM; fasting plasma glucose ≥ 7.0 mmol/L or 2-hour plasma glucose ≥ 11.1 mmol/L. In supplementary analyses patients with prediabetes or T2DM were categorised as having abnormal glucose tolerance.

3.4  **Sleep registration, device descriptions and definitions**

Portable monitors were used for somnography so that each patient could be monitored in their natural sleeping habitat with their everyday pre-bed rituals. To avoid inter-rater variation all recordings were manually scored by the same person (Jan Magnus Fredheim).

3.4.1 **Embletta™**

We used Embletta™, a type II portable nine channel somnograph, for sleep registrations in all papers. Portable sleep diagnostic systems like the Embletta™ have a high sensitivity and are considered reliable in the diagnosis of OSA as there are few false positive results compared to polysomnography. Although a type II portable monitor, we did not utilize the EEG or the ECG option in our studies, so for practical purposes it functioned as a type III monitor.

Patients received both written and oral instructions regarding Embletta™ equipment usage. Patients equipped themselves and registrations were manually scored the following day. Treatment was provided according to current guidelines. Patients already using CPAP had a one week wash-out period prior to the sleep registration where they did not use the machine.

An apnea event was defined as a 90% or more reduction in baseline nasal air flow lasting at least ten seconds. Hypopnea events were defined as a 50% - 90% decrease in pre-event nasal air flow lasting ≥ 10 seconds accompanied by at least a 3% drop in oxygen saturation and/or signs of awakening or increased stress. Both supine and non-supine values
of AHI were recorded given that these might have clinical implications. Oxygen desaturation index (ODI) was defined as the number of episodes with at least a 3% drop in oxygen saturation per hour. Oxygen saturation (SPO2) in terms of both mean and lowest value through the night were measured by the finger pulse oxymeter.

OSA was addressed as both a continuous (AHI) and categorical variable (OSA; yes/no, if yes: mild, moderate, severe). Other outcome variables were resolution of OSA (AHI cut off 5) and improvement of moderate or severe OSA (AHI≥15) to mild or no OSA. OSA was categorized as mild (AHI 5-15 events/hour), moderate (AHI15-30 events/hour) or severe (AHI ≥30 events/hour). Scoring rules were in accordance with the 2007 American Academy of Sleep Medicine (AASM) manual for the scoring of sleep ⁵.

### 3.4.2  ApneaLink™

In paper III Embletta™ was used as the reference method when we validated ApneaLink™ with three channels. The ApneaLink™ is a type IV portable somnograph with three channels (nasal airflow, pulse and oxygen saturation). The recorder is worn around the chest and a nasal cannula and pulse oximetry is attached to it. The internal memory and battery allow approximately 10 hours of recording. Accompanying software analyzes the recording and presents the data in a one-page report. The AHI is calculated based on total study time. It is possible to manually score the data, but the automatic report was the basis of our investigations. In our analyzes we used the automatic scoring algorithm to explore whether a non-sleep specialist can trust the automatic report produced by the device. The default software settings were used. These defined an apnea as a reduction of nasal flow by at least 80% of baseline lasting ten seconds or more. Hypopneas were defined as a decrease in nasal flow by 50-80% of baseline for ≥10 seconds. The maximum possible duration of an apnea was 80 seconds and the maximum possible duration of a hypopnea was 100 seconds. If apneas or hypopneas lasted longer than this it was automatically interpreted by the software as an artifact.
3.5 Laboratory analyses (paper I)

Blood sampling was performed either in a fasting state or during an oral glucose tolerance test (OGTT)\textsuperscript{134}. Standard 75 gram OGTTs with blood samples taken before and 120 minutes after ingestion of glucose were performed, with an additional sampling at 30 minutes. All blood samples were taken at the Department of Clinical Chemistry at Vestfold Hospital Trust. Samples clotted at room temperature and serum was separated from cells within 30 minutes (OGTT) or 2 hours (fasting samples). Serum samples were stored at either -20°C (analyses performed at the Hormone Laboratory, Oslo University Hospital Aker) or -80°C (analyses performed at the Endocrine Laboratory, Oslo University Hospital Rikshospitalet) or analysed the same day (analyses performed at the Department of Clinical Chemistry at Vestfold Hospital Trust). Spot morning urine samples were collected and analysed the same day.

3.6 Statistics

Data are given as either mean (SD) or proportions (%) unless stated otherwise. Skewed variables were transformed using natural logarithms before statistical analysis. Between group differences were assessed using independent samples t-test or analysis of variance (ANOVA) (continuous data) and Fisher’s exact test (categorical data).

In paper II within-group comparisons were performed using paired samples t-test for continuous variables and McNemar test for dichotomized variables. Between-group differences in outcome variables were assessed using t-test, Fisher exact test, and multiple logistic regression analyses with predefined explanatory variables.

Multiple logistic regression analyses with pre-defined explanatory variables and OSA (yes/no, cut off AHI=5) as the dependent variable were performed in paper I. We fitted one crude (unadjusted) logistic regression model and then stepwise three separate multiple
logistic regression models. The multiple logistic regression analysis was repeated in all models using AHI cut off 15.

To address the issue of multicollinearity, we assessed the variance inflation factor (VIF) in the logistic regression models.

In paper III Bland-Altman plots with corresponding 95% limits of agreement (LoA) were used to assess agreement between the reference instrument and the instrument to be validated (ApneaLink™), as well as agreement between the two nights of ApneaLink™ registrations. The traditional Bland Altman plot assumes that variance in the measurements is constant across the observed range. For data where the variance is proportional to the measured value the limits of agreement will have to be correspondingly wider for higher measurement values than for lower. We applied the log transform to the data for calculation of LoA, with back transformation to original scale for interpretation resulting in diagonal LoA lines. Sensitivity and specificity for diagnosing various categories of OSA (Embletta™ as reference instrument) were calculated for different AHI values from the Apnea Link-studies. Receiver operating characteristics curves (ROC-curves) with corresponding area under the curve (AUC) were constructed to evaluate the diagnostic accuracy and to illustrate the true positive rate (sensitivity) against the false positive rate (1-specificity) at various AHI cut off values (5, 15 and 30).

Data were analyzed by the Statistical Package of the Social Science (SPSS) for Windows, version 16 and 17 (SPSS, Chicago, IL, USA) and R 3.0.1.

3.7 Ethics

3.7.1 Approvals

The Morbid Obesity Biobank Registry has the approval of the regional ethics committee of the Southern Norway Regional Health Authority (reference number S-05175), the Norwegian Social Science Data Service (reference number 14029) and the former Directorate for Health and Social Affairs (reference number 06/530). The MOBIL study was approved by the regional ethics committee of the Southern Norway Regional Health Authority.
and was registered in the ClinicalTrials.gov-registry under the unique trial number NCT00273104. The study was conducted according to the guidelines laid down in the declaration of Helsinki. All patients provided written informed consent.

3.7.2. Funding

The studies in this thesis have been supported by a research fellowship granted by the South-Eastern Norway Regional Health Authority to Jan Magnus Fredheim. Jan Magnus Fredheim also received an unrestricted grant (100,000 NOK) from ResMed Norway. Co-author Dag Hofso has received unrestricted grants from Novo Nordisk A/S, Vestfold Hospital Trust and the South-Eastern Norway Regional Health Authority. None of the authors report a personal or financial conflict of interest.
4 SUMMARY OF RESULTS

4.1 Paper I

Type 2 diabetes and prediabetes are associated with obstructive sleep apnea in extremely obese subjects: A cross-sectional study

A total of 42 (31%) patients had mild OSA, 18 (13%) moderate OSA, and 24 (18%) severe OSA. Further, 39 (29%) subjects had NGT, 58 (42%) prediabetes and 40 (29%) T2DM. Among the patients with NGT, 33% had OSA, while 67% of the patients with prediabetes and 78% of the T2DM patients also had OSA.

BMI did not differ significantly between the various glucose tolerance groups. In contrast, mean age increased with worsening glucose tolerance.

Association between OSA and various measures of glucose tolerance

In a crude, unadjusted logistic regression model (model 1) subjects with prediabetes and T2DM had approximately 4- and 7-fold increased odds of OSA compared with the normoglycemic group (table 2). The odds of OSA among patients with prediabetes and T2DM were attenuated after adjustment for gender, age, BMI, HOMA-IR and high sensitive CRP (models 2-4), but remained statistically significant.

As an addition to model 4 we adjusted for smoking, alcohol consumption, OSA relevant medication (benzodiazepines, tricyclic antidepressants and antipsychotics) and hypertension (systolic and diastolic), with none of these significantly altering the OR of having OSA (data not shown). After replacing AHI cut off 5 (events/hour) with AHI cut off 15 as the dependent variable in the model, glucose tolerance was not significantly associated with $\text{AHI} \geq 15$. 
### Table 2
Odds of obstructive sleep apnea (AHI cut off 5) in extremely obese subjects with type 2-diabetes or prediabetes

Data are given as odds ratio (95 % CI) using multiple logistic regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95 % CI)</td>
<td>OR (95 % CI)</td>
<td>OR (95 % CI)</td>
<td>OR (95 % CI)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>4.4 (1.9-10.6) (^a)</td>
<td>3.3 (1.1-9.4) (^c)</td>
<td>3.2 (1.0-10.1) (^c)</td>
<td>4.0 (1.2-13.2) (^c)</td>
</tr>
<tr>
<td>Type 2-diabetes</td>
<td>6.9 (2.5-18.7) (^a)</td>
<td>4.3 (1.3-14.7) (^c)</td>
<td>4.3 (1.2-16.4) (^c)</td>
<td>5.4 (1.3-21.5) (^c)</td>
</tr>
<tr>
<td>Gender</td>
<td>5.3 (1.7-17.1) (^b)</td>
<td>5.0 (1.5-16.5) (^b)</td>
<td>4.2 (1.2-14.4) (^c)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.15 (1.08-1.21) (^a)</td>
<td>1.15 (1.08-1.22) (^a)</td>
<td>1.15 (1.08-1.21) (^a)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.05 (0.97-1.14)</td>
<td>1.05 (0.97-1.14)</td>
<td>1.08 (0.99-1.18)</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.0 (0.8-1.3)</td>
<td>0.9 (0.7-1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.9 (0.7-1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}p≤0.001\) \(^{b}p≤0.01\) \(^{c}p<0.05\)

#### 4.2 Paper II

**Obstructive sleep apnea after weight loss: a clinical trial comparing gastric bypass and intensive lifestyle intervention**

At baseline 84 patients (63%) had OSA (32% mild, 13% moderate, and 18% severe). The prevalence of mild, moderate, and severe OSA did not differ significantly between treatment groups (**p = 0.159**). The RYGB patients were significantly heavier and younger than the ILI patients (table 3).

Compared with baseline, the prevalence of OSA was significantly lower after treatment in both the ILI-group (46% vs 68%) and the RYGB-group (20% vs 60%). In
addition, a significant number of patients changed from an AHI \( \geq 15 \) events/h (requiring CPAP) at baseline to AHI <15 (not requiring CPAP) at follow-up: 19 subjects (73%) in the RYGB group and 8 subjects (53%) in the ILI group, within-group difference, \( p < 0.001 \) and 0.039, respectively, between-group difference \( p = 0.306 \).

OSA severity among the 84 patients with OSA at baseline reduced in both groups, although significantly more in the RYGB group than in the ILI group (Table 3). AHI reduced significantly more in the RYGB than in the ILI group, mean between group difference (95% CI) 7.2 (4.4, 21.2) events/h, \( p = 0.003 \). BMI-change correlated significantly with the change in AHI, \( r = 0.273, p = 0.001 \).

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=40)</th>
<th>Within-group changes</th>
<th>Between group differences p-value***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lifestyle</td>
<td>Surgery***</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.3 (8.9)</td>
<td>46.5 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Gender % (male/female)</td>
<td>38/62</td>
<td>43/57</td>
<td></td>
</tr>
<tr>
<td>Anthropometric measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>43.9 (5.3)</td>
<td>47.5 (5.6)</td>
<td>-4.2 (-5.4, -2.9)*</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>127.4 (19.6)</td>
<td>141.5 (20.5)</td>
<td>-12.1 (-16.0, -8.3)*</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>41.8 (4.4)</td>
<td>43.9 (3.7)</td>
<td>-0.3 (-2.2, 1.6)</td>
</tr>
<tr>
<td>Sleep registration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (events/h)</td>
<td>21.8 (20.9)</td>
<td>29.3 (24.1)</td>
<td>-8.8 (-14.2, -3.4)**</td>
</tr>
<tr>
<td>ODI (events/h)</td>
<td>19.9 (16.1)</td>
<td>30.2 (24.6)</td>
<td>-10.6 (-16.2, -1.1)**</td>
</tr>
<tr>
<td>Snoring (% of night)</td>
<td>19.5 (21.5)</td>
<td>24.2 (23.2)</td>
<td>-5.2 (-12.5, 2.1)</td>
</tr>
<tr>
<td>SpO² (%)</td>
<td>92.6 (3.4)</td>
<td>92.8 (2.5)</td>
<td>0.8 (-0.4, 1.9)</td>
</tr>
<tr>
<td>Lowest O2</td>
<td>78.0 (8.2)</td>
<td>75.8 (9.4)</td>
<td>4.0 (1.3, 6.7)**</td>
</tr>
<tr>
<td>Supine AHI</td>
<td>23.6 (22.3)</td>
<td>41.5 (31.4)</td>
<td>-5.4 (-12.4, 1.6)</td>
</tr>
<tr>
<td>Non supine AHI</td>
<td>21.7 (23.9)</td>
<td>25.9 (28.3)</td>
<td>-10.2 (-17.0, -3.3)**</td>
</tr>
</tbody>
</table>

*p < 0.001

**=p-value < 0.05

*** between-group difference

Data are presented as number (%) or mean (SD or 95 % CI).
Table 3 - Sleep registration and anthropometric characteristics in 84 morbidly obese patients with OSA (AHI≥5), at baseline and 1-year follow up, according to treatment group; intensive lifestyle intervention or Roux-en-Y gastric bypass surgery.

At follow-up, remission of OSA (AHI <5 events/h) was registered in 29 of 44 (66%) RYGB patients and 16 of 40 (40%) ILI patients, between group difference p = 0.028. Another 5 (13%) ILI patients and 7 (16%) RYGB patients improved to a less severe level of OSA at follow-up (figure 4). A total of 3 patients in the ILI group and one in the RYGB group deteriorated from no OSA to mild OSA. One RYGB patient and two ILI patients with mild OSA deteriorated to moderate OSA, and one patient in the ILI group deteriorated from moderate to severe OSA. AHI was reduced, with 0.93 events/h per kg weight reduction in the ILI group and 0.52 in the RYGB group, mean between-group difference (95% CI) 0.41 (−0.6, 1.4), p = 0.405.
Figure 4 – Percentage distribution of change in OSA category (none, mild, moderate or severe) of 84 morbidly obese OSA patients treated with either intensive lifestyle intervention (ILI, 40 patients) or Roux-en-Y gastric bypass surgery (RGB, 44 patients).

Treatment choice was an independent predictor of the presence of OSA (AHI ≥5 events/h) at one year after adjusting for age, gender and baseline AHI. The surgical patients had a 67% lower odds of OSA at one year (OR [95% CI] 0.33 [0.14, 0.81], p = 0.015). After adding BMI change to this model treatment group assignment was no longer significant: OR (95% CI) 1.31 (0.32, 5.35), p = 0.709. There was no significant interaction between gender and treatment group in this multivariate logistic regression model adjusted for age, gender, baseline AHI and BMI change.

4.3 Paper III
Validation of a portable monitor for the diagnosis of obstructive sleep apnea in morbidly obese patients

We aimed to validate the diagnostic accuracy and night-to-night variability of a simple three channel (type IV monitor) sleep registration device, ApneaLink™ (AL) in a population of morbidly obese subjects.

The patients (n=105) underwent two successive nights of recordings; the first night with the AL only, and the following night with both the reference instrument Emblettà™ (E), a type II portable somnograph with nine channels, and the AL.

A total of 63 patients (60%) had OSA as diagnosed by the reference instrument (E). A total of 29 subjects had mild OSA, 12 subjects had moderate OSA and 22 severe OSA. Men had a significantly higher prevalence and severity of OSA than women.
The mean AHI, oxygen desaturation index (ODI) and peripheral oxygen saturation (pO2) did not differ significantly between the three measurements.

Bland-Altman plot with diagonal limits of agreement (LoA) showed narrow LoA for small AHI values and overall the plot showed good agreement between the two methods. The mean difference between the measurements was close to zero indicating little systematic bias between the two apparatus. AL had a tendency to slightly overestimate AHI at smaller values.

The Bland-Altman showed good agreement between AHI values for the two AL registrations and a mean difference between methods close to zero.

The sensitivity and specificity of the AL were 93% and 71% at the AHI cut-off 5 events/hour and 94% and 94% at the AHI cut-off 15, respectively. The night-to-night variability was low.

The AL misclassified 12 non-OSA patients (E-AHI<5) to have OSA, all of whom were categorized as having mild OSA. Further, 4 OSA patients (E-AHI≥5) with E-AHI range 5.9-7.6 were misclassified as non-OSA. All patients with severe OSA (AHI≥30) were identified by the AL.

The diagnostic accuracy of AL was high at all levels of OSA (mild, moderate, severe, all areas under the curve (AUC) >0.94).
The main results of the papers included in this thesis support the following hypotheses: 1) T2DM and prediabetes are associated with OSA in extremely obese patients. 2) Gastric bypass surgery is more effective at reducing the prevalence and severity of OSA than intensive lifestyle intervention, and this effect seems to be mediated through weight loss. 3) A simple three channel sleep registration device, ApneaLink™, has a high diagnostic accuracy in terms of diagnosing OSA in treatment seeking morbidly obese patients.

This section of the thesis will discuss methodological aspects, limitations, compare the results with other studies and state possible clinical implications of the findings as well as suggest topics for future research.

5.1 Methodological considerations

5.1.1 Study designs and statistics

The different study designs of the 3 papers in this thesis (cross-sectional study, non-randomized controlled clinical trial and validation study) all have their particular strengths and limitations as will be discussed below. Patients included in all three papers were recruited from the Morbid Obesity Centre, which is a tertiary care center at Vestfold Hospital Trust. Taking this into account, the possibility of a sampling bias cannot be excluded. Subjects not seeking medical advice for their morbid obesity and patients who themselves take the initiative of seeking private treatment alternatives might differ from our population in several respects. As our subjects are morbidly or extremely obese (grade III) the results of our findings are not directly applicable to less obese or to normal weight subjects. The study population in all three studies was largely Caucasian, and as such the findings might not be generalizable to non-Caucasian populations.
The prevalence of obesity related comorbidities among morbidly obese with BMI between 35 and 40 kg/m² is higher than in the general population with corresponding BMI, as this is part of the diagnostic criteria. In paper I we analysed the occurrence of OSA in morbidly obese patients with prediabetes and T2DM. To reduce the possible selection bias among the patients with BMI 35 – 39.9 kg/m² (obesity grade II), among whom the prevalence of T2DM would be artificially high, only patients with obesity grade III (BMI ≥ 40 kg/m²) were included. Since this study had a cross-sectional design it cannot be used to verify any causal relationship between T2DM and OSA. Given the current understanding of the pathophysiology of both OSA and T2DM our results do, however, allow speculation as to how T2DM and prediabetes might increase the risk of OSA.

One of the strengths of this study is the relatively high number of extremely obese subjects with a high prevalence of abnormal glucose tolerance and OSA. Using the data we also made gender specific calculations as to the prevalence of OSA among various glucose categories. Females were divided into two groups given that there is a difference in OSA prevalence among pre- versus postmenopausal women. However, stratification of data generally weakens the power of statistical analyses. This might have affected our results, as in paper I where we found no statistically significant difference in OSA prevalence between the different glucose categories among morbidly obese men or postmenopausal women. This finding might represent a type-II error, but is on the other hand in agreement with results from the Sleep AHEAD study where OSA prevalence significantly increased with the worsening of glucose tolerance in premenopausal women but not in postmenopausal women. Another example from paper I where stratification could have weakened the result might be the analyses of leptin. We found lower leptin levels among patients with OSA than among non-OSA patients, a finding that contrasts with most other studies. Males do in general have lower leptin levels than females, and as the male proportion of OSA patients was quite high, that might partly explain the finding. We could, however, not find a gender difference between patients with and without OSA, potentially undermining the above explanation.
there were only seven males without OSA a type-II error might be an explanation for the non-significant leptin difference.

Paper II

At the time of publication there were, to the best of our knowledge, no other prospective clinical trials comparing the effects of bariatric surgery and intensive lifestyle intervention on the severity or resolution of OSA. The study is based on follow-up data (1-year) from the MOBIL study.

The MOBIL study was a non-randomized pragmatic clinical trial. In this context pragmatic means “practical”. The study design may infer reduced internal validity compared to a randomized design. The lack of randomization might lead to treatment allocation bias in particular. Subjects choosing intensive lifestyle intervention before surgery might be more motivated to say physical activity and a healthier diet. The two intervention groups were also different in terms of weight and age; patients in the surgery group were younger and heavier. The lack of randomization was, in light of ethical and legal concerns, considered unethical\textsuperscript{104}. Our center is a public health care provider, and according to national guidelines patients should be offered either conservative or surgical therapy in an obesity clinic based on the multidisciplinary team model\textsuperscript{129}. Randomization to surgery would therefore be questioned if the patient both wanted and qualified for a lifestyle intervention programme and vice versa. To be able to carry out a study comparing the two treatment options we had to adapt the study to the clinical everyday, not vice versa. This is the main reason we chose a practical (pragmatic) approach as opposed to a randomized trial design.

One limitation of the study is the lack of registration of patient CPAP-usage and physical activity levels. Sedative drug and alcohol intake, both of which affect the degree of OSA, were also not recorded.
This study was a cross-sectional validation and diagnostic accuracy study. We validated the diagnostic accuracy and night-to-night variability of a simple sleep registration device, ApneaLink™, in a population of morbidly obese subjects. One of the strengths of this study is the relatively high number of participants (n=105). The gold standard of sleep registration is polysomnography (PSG). PSG is not available at our hospital, hence we utilized our existing equipment, Embletta™, as the reference method. Type II and III monitors (as the Embletta™) are by far more common in use in Norway than type I monitors (PSG). The agreement between Embletta™ and PSG has been shown to be good in validation studies\textsuperscript{131,132}. We thus deemed it legitimate to use Embletta™ as the reference method in this validation study.

### 5.1.2 Sleep registration and diagnostic criteria

Any method of sleep registration demands some sort of intervention, thereby interfering with the natural sleep pattern. The gold standard method is polysomnography, where the patients are admitted and monitored over the course of an entire night's sleep. This method is, however, expensive, time consuming and removes the patient from his/her natural sleep environment. Since our sleep registration equipment lacked EEG, we were not able to determine sleep time and sleep stages. Our calculation of AHI is therefore not based on actual sleep time but rather time in bed. All patients filled out a mandatory sleep diary ahead of the night where their sleep was to be registered, enabling us to decide when the patient slept. The advantage of portable monitors such as Embletta™ is that they allow the patient to maintain their normal sleep environment and pre-bed rituals.

In our studies we used only a limited number of the available Embletta™ channels, meaning in practical terms that it was comparable to a type III monitor, although originally being a type II monitor.
The advantages of ApneaLink™ and other portable monitors compared to PSG include the cost-effectiveness and the fact that more patients might be diagnosed early, leading to substantial economic savings through the prevention of morbidity, accidents and absenteeism/presenteeism\textsuperscript{138}. Compared to more elaborate equipment the AL is practical to use, easy to interpret and its size and simplicity helps facilitate a more natural sleep and usage by non-specialists.

5.1.3 Epworth Sleepiness Scale

To evaluate daytime sleepiness we used the Norwegian translation of the Epworth Sleepiness Scale (ESS). This Norwegian version was validated by Beiske et al in 2009\textsuperscript{139}. They found that the internal consistency reliability, as assessed with Cronbach’s alpha, was 0.84 (n=154). Test–retest reliability for the eight ESS items ranged from weighted kappa of 0.61 to 0.80 (n=50) for the total score. Intra Class Correlation was 0.81.

ESS is a subjective measure of daytime sleepiness, with multiple sleep latency test (MSLT) being the objective means of measurement. This test is based on the principle that degrees of sleepiness can be measured in terms of how quickly one falls asleep (sleep latency) when given the opportunity to do so. The association between ESS and MSLT is, however, quite poor, with the two tests arguably evaluating different but complementary aspects of sleepiness\textsuperscript{140}. In our studies we used subjective daytime sleepiness as measured by ESS.

5.2 General discussion on specific findings

5.2.1 Obstructive sleep apnea and glucose intolerance

Our main finding in paper I was that extremely obese patients with T2DM and prediabetes had higher odds of OSA compared with normal glucose tolerance subjects. This finding was statistically significant even after adjustment for age, gender, BMI, insulin resistance, inflammation, hypertension, smoking, alcohol consumption and medication. The
evidence relating OSA to T2DM was strong enough to convince the International Diabetes Foundation to publish a consensus statement in 2008 outlining the need to screen for OSA in diabetes clinics. Since the consensus statement there has been an increasing recognition that obstructive sleep apnea (OSA) is associated with incident T2DM. A recently published meta-analysis of available prospective cohort studies as of March 2012 confirms this. Six studies with a total of 5953 participants, with follow-up periods of 2.7–16 years and 332 incident cases of T2DM showed that moderate-severe OSA was associated with a greater risk of T2DM (RR 1.63; 95% confidence interval (CI): 1.09–2.45), as compared with the absence of OSA. For subjects with mild OSA the pooled RR of developing T2DM was 1.22 (95% CI: 0.91–1.63). These findings support the notion/hypothesis that OSA may lead to T2DM.

As paper I is a cross-sectional study causality cannot be inferred. Nevertheless, it can be speculated that there might be a bidirectional causal relationship between OSA and T2DM. Previous cross-sectional studies examining the relationship between OSA and glucose metabolism have mainly focused on the prevalence of T2DM and impaired glucose metabolism among subjects with OSA compared to subjects without OSA. Few studies have addressed OSA among subjects with established T2DM. The reported prevalence rates of OSA in diabetic populations range from 23% to 86%.

It is well known that immune activation and subsequent increase in the circulating concentration of pro-inflammatory cytokines are associated with both adipose tissue and T2DM. Both these factors may play a role in the pathogenesis of OSA. T2DM is thus a condition which produces general inflammation. The increased mucosal thickness in the upper airways, secondary to general inflammation caused by T2DM, may contribute to airway narrowing and promote collapse of upper airways. According to our hypothesis this is one of two pathways by which T2DM may lead to OSA.

The second part of our theory is based on the fact that the patency of the upper airways is largely dependent upon a well functioning nerve (vagal nerve), neuromuscular
juncture and muscle (pharyngeal dilators). Patients with T2DM have increased risk of neuropathy in the autonomic nervous system as well as in the extremities. Impaired vagal activity due to diabetic autonomic neuropathy may lead to dysfunction of upper airway muscles and increased risk of OSA. This theory is supported by the fact that respiratory disturbances are more frequent during rapid eye movement (REM) sleep when the tone of the UA dilator muscles is reduced. The autonomic contribution to maintaining a patent airway is therefore substantial. Diabetic autonomic neuropathy is a common complication of T2DM, but many patients are not aware of it because of multi-organ involvement and insidious onset. Because of varying diagnostic criteria there are big differences in the prevalence estimates of diabetic autonomic neuropathy. A study by Bottini et al of non-obese adults with diabetic autonomic neuropathy and postural hypotension showed a frequency of obstructive sleep apnea-hypopnea >30 percent. In obese subjects, diabetic autonomic neuropathy is also associated with an increased risk of obstructive sleep apnea compared with other obese subjects with or without T2DM. To conclude, T2DM might increase the risk of developing OSA via two mechanisms; by inflammation and by impairment of the autonomic nervous system controlling the UA dilator muscles.

5.2.2 Obstructive sleep apnea and weight reduction

In paper II we conclude that gastric bypass surgery is more effective than intensive lifestyle intervention at reducing the prevalence and severity of OSA in morbidly obese. Obviously one could argue that there is a big difference in weight loss between the two groups; the surgery group lost around 30% of their body weight and the lifestyle group around 10%. After multivariate analyses adjusting for weight loss there was no difference between the two treatment groups, suggesting that weight loss mediated the beneficial effects of surgery. Just after submission of paper II, a randomized controlled trial comparing surgical versus conventional therapy for weight loss treatment of obstructive sleep apnea was published. The study included 60 obese patients with an AHI of 20 events/hour or
more. Patients were randomized to a conventional weight loss programme or to bariatric surgery (gastric banding). Follow up was at 2 years compared to our one-year follow up, and the surgical procedure was different from that undertaken in our study. The expected weight loss after gastric banding was less than after gastric bypass, with mean (SD) excess weight loss after 10 years of $69 \pm 29\%$ versus $46 \pm 27\%$, respectively, $p = 0.03^{147}$. The surgical group achieved a significantly greater mean weight loss than the conventional group. Despite major differences in weight loss between the two treatment groups in the JAMA article there was statistically no greater reduction in AHI in the favor of surgery. In our study we performed subanalyses of patients with AHI $\geq 15$ events/hour at baseline. As in the article by Dixon et al, we did not find any difference between this subgroup and treatment groups improving their AHI to < 15 events/hour at follow-up. Still, we cannot rule out this being a type-II error – a failure to prove a difference between groups due to low number of study subjects.

In a large randomized controlled trial study of the effects of weight loss on OSA in obese subjects with T2DM (the Sleep AHEAD study), weight loss produced by intensive lifestyle intervention significantly improved OSA as measured by AHI$^{101}$. The control group were assigned to 3 group sessions related to effective diabetes management. The intensive lifestyle intervention participants lost more weight at 1 year than did DSE participants (10.8 kg vs 0.6 kg; $P < .001$). At 1 year, more than 3 times as many participants in the intensive lifestyle intervention group than in the control group had total remission of their OSA. Initial AHI and weight loss were the strongest predictors of changes in AHI at 1 year ($P<.01$). As in our study, the greatest improvement in OSA was observed in the participants who lost the most weight.

One conclusion to draw from these two studies is that conventional means (i.e. lifestyle intervention) of intervention are also an effective means of reducing the severity of moderate and severe OSA.
5.2.3 Obstructive sleep apnea and leptin

In paper I we found lower leptin levels in OSA patients than in non-OSA patients, although this is an uncertain finding given that it might be the result of a type-II error. Leptin is a hormone that contributes to satiety perception and is known to decrease with sleep restriction \(^{80}\). There is, however, a difference between sole sleep restriction and sleep disrupted by OSA. Studies of patients with OSA and similarly obese controls show that those with OSA had gained weight in the year preceding the diagnosis and had higher leptin levels than expected based on their percentage body fat \(^{148,149}\), suggesting that OSA is associated with greater resistance to the weight-reducing effect of leptin and not obesity alone. This explains the typical high leptin levels in OSA patients and the coexisting leptin resistance. There are several intervention studies demonstrating a decrease in leptin levels in patients treated with CPAP \(^{150-152}\).

5.2.4 ApneaLink™ as a diagnostic tool

A 2007 portable monitoring task force report was published in AASM’s own journal, Journal of Clinical Sleep Medicine, exploring the role of portable monitors in sleep diagnostics\(^ {153}\). They concluded that portable monitors may be used as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA on the condition that it is used in conjugation with a comprehensive sleep evaluation. Patients in our population had a high pretest probability of moderate to severe OSA. The task force did not recommend type IV monitors such as the monitor we validated. In our population of morbidly obese the agreement between the reference method and ApneaLink™ was good. The sensitivity and specificity of the instrument were 93% and 71% at the AHI cut-off 5 events/hour and 94% and 94% at the AHI cut-off 15. In Norway, waiting lists for sleep registrations are generally long and few places offer PSG. In a clinical setting, our results indicate that monitors like the ApneaLink™ are safe to use as a diagnostic tool in morbidly obese subjects with suspected OSA. In accordance with the 2007 task force, this
tool should not be used in subgroups with significant comorbidities such as moderate to severe pulmonary disease, neuromuscular disease and congestive heart failure. Morbidly obese with massive central obesity must also be evaluated for obesity hypoventilation syndrome, where suspicion of this should lead to an examination of an arterial blood analysis to discover hypercapnia. In cases of doubt, where clinical signs of OSA are prominent despite an AHI<5 events/hour, the recording might be repeated or more elaborate somnographs might be used. In most cases a patient diagnosed with OSA is treated with CPAP. A modern CPAP delivers sufficient data to evaluate whether a patient needs a CPAP (because he has no OSA) or a different positive pressure device like a VPAP (in cases of e.g. central apneas or Cheyne-Stokes respiration). Being able to bypass the more elaborate sleep registration methods for some patient groups might lower costs and reduce waiting lists.

Our finding that the AL had a high diagnostic sensitivity in terms of the identification of subjects with OSA (AHI ≥ 5) is in accordance with previous validation studies of normal weight to overweight populations and adolescents. Importantly, we report a somewhat higher specificity than previous studies.

The high sensitivity of the AL in the diagnosis of patients with moderate to severe OSA is in accordance with previous studies. The specificity regarding the diagnosis of moderate or severe OSA was, however, higher in our study compared to those reported by others, and the predictive value of a positive test was higher or equal to others. In addition, our validation study of AL with three channels (airflow, oximetry and pulse) showed better sensitivity, specificity and positive predictive value than previous studies of moderately obese subjects where AL had only one channel.

The mean difference between the two ApneaLink™ recordings was close to zero, indicating a low night to night variability. A classic first night effect (FNE) is characterized by increased sleep onset latency, increased REM latency, a lower percentage of REM stage sleep and lower sleep efficiency as measured by polysomnography (PSG). The FNE typically leads to a lower AHI the first night compared to AHI measured the second night. FNE is a
phenomena described when PSG is performed in-hospital, where environmental change (hospital bed versus own bed) and elaborate equipment affects sleep, particularly on the first night of repeated measures. Despite two consecutive nights of recordings we did not identify any first night effect (FNE). This is in accordance with other studies suggesting there is no significant FNE in portable sleep monitoring, although these studies are relatively few \textsuperscript{163,164}. The largest study of the night to night variability of home sleep testing by Stepnowsky examined the AHI in a retrospective comparison of 3 sequential nights in 1091 patients and found that 10% were misclassified on night 1 relative to the highest AHI level\textsuperscript{165}.

5.3 Clinical implications

We showed that both prediabetes and T2DM are associated with OSA in extremely obese subjects. In accordance with the recommendations from the International Diabetes Federation (IDF) all subjects with T2DM should be screened for OSA. Our results, if verified by others, suggest that it might also be appropriate to screen severely obese subjects with prediabetes for OSA.

Gastric bypass surgery was more effective than intensive lifestyle intervention at reducing the prevalence and severity of OSA in a population of treatment seeking morbidly obese patients, and the beneficial effect of surgery seemed to be mediated by weight loss. Weight reduction using any method should have a high priority in the treatment of obstructive sleep apnea in morbidly obese patients.

The simple three channel sleep registration device ApneaLink™ has a high diagnostic accuracy in diagnosing OSA in morbidly obese treatment seeking patients. Accordingly, this and similar instruments might help non-specialists to diagnose OSA in morbidly obese patients, and, importantly, help non-specialists to refer patients who need specific treatment to a specialist without unnecessary delay.
5.4 Topics for future research

In paper I we hypothesized that T2DM might cause OSA through at least two different pathways. This is yet to be confirmed by other studies, and is a potential research avenue. The association between prediabetes and OSA needs verification and further study.

There are very few prospective studies comparing lifestyle intervention weight loss and bariatric surgery weight loss, and we would encourage such studies in the future in order to explore differences between surgical and non-surgical weight loss methods.
6 CONCLUSIONS

In paper I we showed that prediabetes and T2DM are associated with OSA in extremely obese subjects. Our findings support the recommendations of the International Diabetes Federation (IDF), which suggest that subjects with T2DM should be screened for OSA. If the relationship between prediabetes and OSA is verified by others this may then indicate that obese subjects with prediabetes should also be screened for OSA.

Gastric bypass surgery was more effective than intensive lifestyle intervention at reducing the prevalence and severity of OSA in a population of treatment seeking morbidly obese patients. The beneficial effect of surgical treatment seemed to be mediated by weight loss rather than RYGB per se. Intensive lifestyle intervention was also associated with significant improvements in OSA. Weight reduction should have a high priority in the treatment of obstructive sleep apnea in morbidly obese patients.

The results from paper III indicate that a simple three channel sleep registration device (ApneaLink™) has a high diagnostic accuracy in terms of the diagnosis of OSA in treatment seeking morbidly obese patients. Accordingly, this and similar instruments might help non-specialists to diagnose OSA in morbidly obese patients, and, importantly, help non-specialists to refer patients who need specific treatment to a specialist without unnecessary delay.
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Type 2 diabetes and pre-diabetes are associated with obstructive sleep apnea in extremely obese subjects: A cross-sectional study

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Abstract

Background: Obstructive sleep apnea (OSA) is a common yet underdiagnosed condition. The aim of our study is to test whether prediabetes and type 2 diabetes are associated with obstructive sleep apnea (OSA) in extremely obese (BMI ≥ 40 kg/m²) subjects.

Methods: One hundred and thirty seven consecutive extremely obese patients (99 females) from a controlled clinical trial (MOBIL-study (Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention Study) (ClinicalTrials.gov number NCT00273104) underwent somnography with Embletta® and a 2-hour oral glucose tolerance test (OGTT). OSA was defined by an apnea-hypopnea index (AHI) ≥ 5 events/hour. Patients were categorized into three groups according to criteria from the American Diabetes Association: normal glucose tolerance, pre-diabetes and type 2 diabetes. Multiple logistic regression analysis was used to identify possible determinants of OSA.

Results: The patients had a mean (SD) age of 43 (11) years and a body mass index (BMI) of 46.9 (5.7) kg/m². Males had significantly higher AHI than females, 29 (25) vs 12 (17) events/hour, p < 0.001. OSA was observed in 81% of men and in 55% of women, p = 0.008. Twenty-nine percent of subjects had normal glucose tolerance, 42% had pre-diabetes and 29% had type 2 diabetes. Among the patients with normal glucose tolerance 33% had OSA, while 67% of the pre-diabetic patients and 78% of the type 2 diabetic patients had OSA, p < 0.001. After adjusting for age, gender, BMI, high sensitive CRP and HOMA-IR, both pre-diabetes and type 2 diabetes were still associated with OSA, odds ratios 3.18 (95% CI 1.00, 10.07), p = 0.049 and 4.17 (1.09, 15.88), p = 0.036, respectively. Mean serum leptin was significantly lower in the OSA than in the non-OSA group, while other measures of inflammation did not differ significantly between groups.

Conclusions: Type 2 diabetes and pre-diabetes are associated with OSA in extremely obese subjects.

Trial registration: MOBIL-study (Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention Study) (ClinicalTrials.gov number NCT00273104)

Keywords: Obstructive sleep apnea, type 2 diabetes, prediabetes, oral glucose tolerance test, inflammation

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Introduction
Obstructive sleep apnea (OSA) is an under-diagnosed yet common disease [1] which is associated with increased incidence of cardiovascular disease and substantially increased risk of death [2,3]. There is a strong relationship between OSA and obesity [4,5], indeed, approximately 70% of patients with OSA are obese [6]. Obesity related subcutaneous and periluminal fat deposits may alter compliance of upper airway walls and narrow the luminal area, thus increasing the likelihood of airway collapse when exposed to the intraluminal negative pressure caused by inspiration [5].

OSA is also associated with increased risk of type 2 diabetes (T2DM) [7,8]. Several mechanisms, including intermittent hypoxia, sleep fragmentation and immune activation may contribute to this association [8-11]. Both adipose tissue and diabetes are associated with immune activation and subsequent increase in the circulating concentration of pro-inflammatory cytokines [12,13], which in turn may play a role in the pathogenesis of OSA.

All dilator muscles of the upper airways are innervated by the vagal nerve, with patency of the upper airway during sleep depending on well functioning nerve, neuromuscular junction and muscle. Diabetes increases the risk of neuropathy in the autonomic nervous system as well as in the extremities [14]. Impaired vagal activity may lead to dysfunction of upper airway muscles and increased risk of OSA [15].

Visceral obesity, high insulin levels and insulin resistance have been associated with increased risk of OSA [16,17]. Some studies have shown a high prevalence of T2DM and pre-diabetes (preDM) in obese subjects with OSA [17-20], indicating that OSA may cause glucose intolerance [17].

We aimed to investigate whether extremely obese subjects with T2DM and preDM have higher odds of OSA than their counterparts with normal glucose tolerance.

Methods
Study design
This is a pre-defined, cross-sectional analysis of baseline data from a controlled clinical trial [MOBIL-study (Morbid Obesity treatment, Bariatric surgery versus Intensive Lifestyle intervention Study) (ClinicalTrials.gov number NCT00273104)] [21]. The study design and setting have previously been described in detail [22]. A brief summary of materials and methods is given below.

Setting/Participants
All participants were recruited from the Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway. The study protocol had the approval of the regional ethics committee and all patients provided written informed consent. Only patients with extreme obesity (obesity grade III; BMI ≥ 40 kg/m²) were included in the present study. Of the 181 patients screened for participation in the MOBIL-study [21], 35 patients were excluded due to a BMI < 40 kg/m² (n = 32) or a missing oral glucose tolerance test (OGTT; n = 3). After the exclusion of an additional nine patients who failed to comply with sleep registrations, 137 extremely obese patients (101 females) were included in the present analysis (figure 1).

Variables and definitions
The primary outcome variable was OSA, which was defined as at least five apneas or hypopneas, lasting more than ten seconds, per hour. The main explanatory variable was glucose tolerance (categorised as normal glucose tolerance (NGT), preDM and T2DM) according to the American Diabetes Association classification 2010 [23]). Other explanatory variables and possible confounders were age, gender, anthropometric measures, smoking, alcohol consumption, hypertension, relevant medication, insulin resistance (as measured by

Figure 1 Flow chart of 181 patients screened for participation in the MOBIL-study. Initially three patients were excluded due to a BMI < 35 kg/m² and nine due to failed sleep registrations. Twenty nine of these patients had a BMI < 40 kg/m² and three had a missing OGTT, thereby leaving 137 extremely obese patients for inclusion in the present analysis.
HOMA-IR) and high sensitivity CRP (hsCRP). Arterial hypertension was defined by systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 or the use of antihypertensive medication. Microalbuminuria was defined as albumin-creatinine ratio ≥ 3 mg/mmol and < 30 mg/mmol, and manifest proteinuria as albumin-creatinine ratio ≥ 30 mg/mmol.

A computer based homeostasis model assessment of insulin resistance (HOMA-IR) was used, HOMA Calculator v2.2.2 [24].

Data sources/measurement

The reference standard method of sleep registration is polysomnography, whereby patients are admitted and monitored during an entire night’s sleep. This method is, however, both time consuming and expensive, and removes the patient from his/her natural sleep environment. Portable monitors, on the other hand, can be used at home and are simple to function. This enables the patient to maintain normal sleep environment and pre-bed rituals [26]. The accuracy of home sleep diagnostic systems like the Embletta™ is considered to be sufficient for most patients in the diagnosis of OSA [27,28]. The night to night variability of sleep-disordered breathing is low, and a retrospective study performed by Stepnowsky et al suggests that one nights recording is sufficient to diagnose OSA in nine out of ten cases [29].

The sleep registrations were performed using Embletta™, a portable multi-channel recorder consisting of a nasal cannula, two piezoelectric belts, a finger pulse oximeter and a body position detector [28]. The two piezoelectric belts were placed around the thorax and abdomen to monitor respiratory movements. To avoid inter-rater variation, Embletta™ recordings were manually scored by the same person [30]. In a study of a large dataset the mean epoch by epoch agreement between scorers for all records was 73% (range 67-82%) [31].

The equipment assembly included both written and oral instructions. The patients equipped themselves prior to going to bed and the registrations were scored the next day. Treatment was provided according to current guidelines [32]. Patients using continuous positive airway pressure prior to the study had a one week wash-out period during which they did not use the machine. All patient data was registered in a Case Report Form (CRF).

All patients, except those with drug-treated T2DM, underwent a standardised OGTT [33]. The patients were categorised into three groups: NGT; fasting plasma glucose <5.6 mmol/L and/or 2-hour plasma glucose <7.8 mmol/L, preDM; fasting plasma glucose 5.6 - 6.9 mmol/L and/or 2-hour plasma glucose 7.8 - 11.0 mmol/L or T2DM; fasting plasma glucose ≥ 7.0 mmol/L or 2-hour plasma glucose ≥ 11.1 mmol/L. In addition, patients with either preDM or T2DM were categorised as to their having abnormal glucose tolerance in supplementary analyses.

Statistical methods

Data are given as either mean (SD) or proportions (%) unless stated otherwise. Between group differences were assessed using independent samples t-test or analysis of variance (ANOVA) (continuous data) and Fisher’s exact test (categorical data). Skewed variables were transformed using natural logarithms before statistical analysis. Multiple logistic regression analyses with pre-defined explanatory variables and OSA (yes/no, cut off AHI = 5) as the dependent variable were also performed [25]. We fitted one crude (unadjusted) logistic regression model (model 1) and three separate multiple logistic regression models (models 2-4). In model 1 glucose tolerance status as a categorical variable was entered as the sole explanatory variable. In model 2 we adjusted for established confounding factors; gender, age and BMI (waist circumference, neck circumference and waist-to-hip ratio were substituted for BMI in supplementary analyses). In model 3 HOMA-IR was added to model 2 to address the possible modifying effect of insulin resistance. In model 4, in order to assess the possible impact of inflammation, hsCRP was added to model 3. In supplementary analyses glucose tolerance as a categorical variable was replaced with HbA1c. The multiple logistic regression analysis was repeated in all models using AHI cut off 15: the recommended clinical cut off for initializing CPAP treatment [32].

To address the issue of multicollinearity we performed calculations of Spearman correlation between categories of glucose tolerance and both HOMA-IR and hsCRP. In addition we assessed the variance inflation factor (VIF) in the logistic regression models. The analyses were performed using SPSS 16.0 (SPSS, Chicago, IL).

Results

A total of 42 (31%) patients had mild OSA, 18 (13%) moderate OSA, and 24 (18%) severe OSA. The prevalence of OSA was higher in men (81%) than in women (55%), p = 0.006, with the severity of OSA more pronounced in males than in females, chi square test p < 0.001 (figure 2). In addition, the prevalence of OSA was...
significantly higher among postmenopausal (26 out of 29, 90%) than premenopausal women (29 out of 72, 40%), p < 0.001.

Demographic, clinical and biochemical characteristics of the 137 extremely obese subjects, according to the presence or absence of OSA, are shown in table 1. Patients with OSA were significantly older, and they had longer neck circumference, higher waist-to-hip ratios and a higher prevalence of comorbid conditions than those without OSA. There were no significant differences between groups regarding smoking and alcohol consumption (table 1).

The prevalence of albuminuria was higher in the OSA group than in the non-OSA group. Mean serum leptin was significantly lower in the OSA than in the non-OSA group, while other measures of inflammation did not differ significantly between groups.

The prescription of analgesics, psychofarmacological drugs, sleep medications and mediation for asthma or chronic pulmonary disease did not differ significantly between groups. In contrast, the proportion of patients using antihypertensive drugs was higher in the OSA-group (34%) than in the non-OSA group (13%), p = 0.009.

Sleep registration data and measures of glucose metabolism of the 137 extremely obese are presented in table 2. Fasting serum glucose, post-challenge serum glucose and HbA1c were significantly higher in the OSA group than in the non-OSA group. There was no significant difference between the two groups regarding s-insulin and HOMA-IR.

OSA according to category of glucose tolerance

A total of 39 (29%) subjects had NGT, 58 (42%) preDM and 40 (29%) T2DM. Among the patients with NGT 33% had OSA, while 67% of the preDM patients and 78% of the T2DM patients had OSA, p = 0.001 and p < 0.001, respectively. The distribution of glucose tolerance categories among different OSA severity categories is shown in table 3.

The proportion of patients with OSA was significantly higher in female patients with preDM or T2DM than in those with NGT, p = 0.004 and p < 0.001, respectively (figure 3). These differences were particularly pronounced in premenopausal women (figure 4).

BMI did not differ significantly between the various glucose tolerance groups: NGT-group mean BMI (SD) 46.5 (4.7) kg/m², preDM-group 47.9 (6.8) kg/m² and the T2DM-group 45.9 (4.8) kg/m², p = 0.220. In contrast, mean age increased with worsening glucose tolerance: NGT-group 39 (11) years, preDM-group 43 (10) years and T2DM-group 46 (5) years, respectively, p < 0.001.

Association between OSA and various measures of glucose tolerance

In a crude, unadjusted logistic regression model (model 1) subjects with preDM and T2DM had approximately 4- and 6-fold increased odds of OSA compared with the normoglycemic group (Table 4). The odds of OSA in preDM and T2DM were attenuated after adjustment for gender, age and BMI (model 2), but remained statistically significant. The substitution of BMI with other anthropometric measures in model 2 did not significantly change the association between abnormal glucose tolerance and OSA (data not shown). Finally, both preDM and T2DM remained associated with significantly higher odds of OSA after further adjustments for HOMA-IR and high sensitive CRP (model 4). Gender and age were both strong predictors of having OSA with ORs (95% CI) of 4.2 (1.2, 14.4) and 1.15 (1.08, 1.21), respectively.

As an addition to model 4 we adjusted for smoking, alcohol consumption, OSA relevant medication (benzodiazepines, tricyclic antidepressants and antipsychotics) and hypertension (systolic and diastolic), with none of these significantly altering the OR of having OSA (data not shown). After replacing AHI cut off 5 (events/hour) with AHI cut off 15 as the dependent variable in the model, glucose tolerance was not significantly associated with AHI ≥ 15.

We tested for correlations between HOMA-IR, hsCRP and glucose tolerance using Spearmans correlation coefficient. HOMA-IR and glucose tolerance had a correlation coefficient of 0.33, p < 0.001. This means a moderate correlation between HOMA and glucose tolerance status, with variation in HOMA-IR explaining 11% of the variation in glucose tolerance. Thus we can safely adjust for HOMA-IR in the logistic regression model. HsCRP and glucose tolerance had a correlation coefficient of 0.03, p = 0.698
PreDM and T2DM were assembled in one group; abnormal glucose tolerance; and replaced with the glucose tolerance categories in the multiple logistic regression model. In model 4 subjects with abnormal glucose tolerance had an OR (95% CI) of having OSA of 4.4 (1.4, 13.8).

Glucose tolerance as a categorical variable was replaced with HbA1c in supplementary logistic regression analyses. HbA1c was not significantly associated with OSA in these models, odds ratio (95% CI) 1.29 (0.79, 2.12, p = 0.314).

Discussion
This study demonstrates that extremely obese patients with type 2 diabetes and prediabetes have higher odds of OSA, even after adjustment for age, gender, overall obesity (BMI), insulin resistance, inflammation, hypertension, smoking, alcohol consumption and medication.

Interpretation
That OSA may cause or worsen glucose tolerance has been firmly established over the last few years [7,17-20,34,35]. Our main objective was, however, to explore the reverse relationship by examining whether extremely obese subjects with abnormal glucose tolerance (preDM or T2DM) had higher odds of OSA. In accordance with Foster et al, we have demonstrated a particularly high prevalence of OSA among severely obese patients with T2DM (78% in our study as compared to 86% in the Foster study) [34]. We extend these

<table>
<thead>
<tr>
<th>Table 1 Anthropometric data and comorbidities in 137 extremely obese subjects according to presence or absence of obstructive sleep apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Gender (male/female)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Smokers</td>
</tr>
<tr>
<td>Alcohol consumption (units/week)</td>
</tr>
<tr>
<td>Anthropometric measures</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Neck (cm)</td>
</tr>
<tr>
<td>Waist (cm)</td>
</tr>
<tr>
<td>Hip (cm)</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
</tr>
<tr>
<td>Blood pressure (mean value, 24-hour ambulatory pressure)</td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Albuminuria</td>
</tr>
<tr>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
</tr>
<tr>
<td>Hypothyreosis</td>
</tr>
<tr>
<td>Anxiety and/or depression</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>Leptin (microg/l)</td>
</tr>
<tr>
<td>Visfatin (ng/ml)</td>
</tr>
<tr>
<td>High sensitive CRP (mg/l)</td>
</tr>
<tr>
<td>Osteoprotegerin (microg/ml)</td>
</tr>
<tr>
<td>Adiponectin (pg/ml)</td>
</tr>
<tr>
<td>IL1Ra (pg/ml)</td>
</tr>
<tr>
<td>Leptin/adiponectin ratio (ng/ml/µg/ml)</td>
</tr>
</tbody>
</table>

Variables are given as either mean (SD) or proportions (%). Statistical analysis: Fisher’s exact test (categorical data), independent samples t-test (continuous data) and Mann-Whitney U test (non-parametric, continuous data).
findings by showing that whilst 2 out of 3 obese patients with preDM had OSA, only 1 out of 3 patients with NGT had OSA. Interestingly, the relationship between glucose tolerance category and OSA was particularly pronounced in premenopausal subjects (figure 4). While less than 20% of the premenopausal patients with NGT had OSA, more than half the patients with abnormal glucose tolerance had OSA. This finding might be a result of the redistribution of adipose tissue to more central parts of the body caused by the hormonal changes during menopause [36]. In older males the prevalence and severity of OSA might decrease because of redistribution of body fat from the central to the peripheral depots. This is possibly a result of lower testosterone levels.

Taking into account the very high prevalence of OSA across glucose categories among morbidly obese men and postmenopausal women, the power of the present study is insufficient to reveal any possible differences between glucose categories. In our study less than one third of patients (29%) had NGT, while 42% suffered from preDM. Two out of three patients with preDM had concomitant OSA. In the light of these figures a considerable proportion of extremely obese subjects could suffer from unrecognized OSA.

The relationship between abnormal glucose tolerance (preDM/T2DM) and OSA might have several explanations. First, it is well established that OSA is associated with insulin resistance and high insulin levels [37]. A causal relationship between these conditions remains, however, to be established [38].

As subjects with abnormal glucose tolerance often have high insulin levels, our results are indirectly supported by a prospective study which demonstrated that high insulin levels were associated with higher incidence of sleep apnea [17]. In women with polycystic ovary syndrome (PCOS) insulin resistance is the strongest predictor of OSA [39]. As insulin resistance seems to be the primary defect in these patients, this could support our findings of an association between preDM, T2DM and OSA. One possible mechanism for these observations may be that the inflammation associated with hyperinsulinemia, insulin resistance and visceral adiposity induces OSA [40]. Inflammation of the upper airways (UA) contributes to narrowing the lumen and thus increases the obstructive tendency.

Although the patients with preDM and T2DM had higher HOMA-IR than those with NGT, adjustments for HOMA-IR did not substantially alter the relationship between glucose intolerance and OSA in our study.

On average the patients with OSA had significantly lower levels of leptin than those without OSA (table 1). As men generally tend to have lower leptin levels than women, this finding might be a result of the redistribution of adipose tissue to more central parts of the body caused by the hormonal changes during menopause [36].

Although this study was cross-sectional in nature, the results suggest that high leptin levels have a protective role against OSA. This is in line with previous reports showing that leptin reduces nocturnal body movements and enhances respiratory effort in response to decreased UA diameter [41].

### Table 2 Sleep registration data and glucose metabolism characteristics in 137 extremely obese subjects according to the presence or absence of obstructive sleep apnea (OSA)

<table>
<thead>
<tr>
<th>Variables</th>
<th>All participants</th>
<th>OSA no</th>
<th>OSA yes</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>137</td>
<td>53 (39%)</td>
<td>84 (61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sleep registration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apnea-Hypopnea index</td>
<td>16 (20)</td>
<td>2 (2)</td>
<td>25 (22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen desaturation index</td>
<td>17 (18)</td>
<td>3 (3)</td>
<td>26 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Snoring (5 of sleep time)</td>
<td>19 (21)</td>
<td>11 (14)</td>
<td>23 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SpO2 (%)</td>
<td>93 (3)</td>
<td>95 (2)</td>
<td>93 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Glucose metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, fasting (mmol/l)</td>
<td>6.6 (2.0)</td>
<td>5.8 (1.1)</td>
<td>7.1 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, 2 hour (mmol/l)</td>
<td>7.6 (3.2)</td>
<td>6.5 (2.5)</td>
<td>8.3 (3.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>HbA1 (%)</td>
<td>5.9 (1.1)</td>
<td>5.5 (0.8)</td>
<td>6.1 (1.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>201 (89)</td>
<td>193 (78)</td>
<td>207 (96)</td>
<td>0.468</td>
</tr>
<tr>
<td>HOMA Insulin Resistance</td>
<td>3.8 (1.7)</td>
<td>3.6 (1.4)</td>
<td>4.0 (1.8)</td>
<td>0.178</td>
</tr>
</tbody>
</table>

Variables are given as either mean (SD) or proportions (%). Statistical analysis: Fisher’s exact test (categorical data) and independent samples t-test (continuous data).

### Table 3 Prevalence of various categories of glucose tolerance according to the presence and severity of obstructive sleep apnea in 137 extremely obese subjects

<table>
<thead>
<tr>
<th>Glucose tolerance status</th>
<th>Non OSA (AHI &lt; 5)</th>
<th>Mild OSA (AHI 5-15)</th>
<th>Moderate OSA (AHI 15-30)</th>
<th>Severe OSA (AHI &gt; 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance</td>
<td>49% (26)</td>
<td>10% (4)</td>
<td>17% (3)</td>
<td>25% (6)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>34% (18)</td>
<td>52% (22)</td>
<td>50% (9)</td>
<td>38% (9)</td>
</tr>
<tr>
<td>Type 2-diabetes</td>
<td>17% (9)</td>
<td>38% (16)</td>
<td>33% (6)</td>
<td>38% (9)</td>
</tr>
</tbody>
</table>

Fredheim et al. Cardiovascular Diabetology 2011, 10:84
http://www.cardiab.com/content/10/1/84

Page 6 of 9
women, the high proportion of men with OSA might partly explain this difference [41]. There was, however, no gender significant difference between the patients with or without OSA in terms of their leptin levels (data not shown). It cannot be ruled out that this is due to a type-II error, encountered because of the low frequency of males without OSA (n = 7).

Our finding of an apparently inverse relationship between leptin and OSA is still to be explored. Some previous studies found a positive correlation between leptin levels and OSA [42,43], whilst others have suggested that the apparent association between OSA and leptin levels is explained by higher BMI [6,11]. By contrast, in our study body weight did not differ significantly between patients with or without OSA.

The pathophysiology of OSA is multi-factorial, the most obvious factor being obesity which is associated with the physical narrowing of the airways. Both adipose tissue and diabetes are known to produce inflammation. Increased mucosal thickness, secondary to general inflammation, may contribute to airway narrowing and collapse. Moreover, diabetic autonomic neuropathy can be a functional factor in OSA by reducing the effectiveness of the UA dilator muscles [15]. This theory is strengthened by the fact that respiratory disturbances are more frequent during rapid eye movement (REM) sleep when the tone of the UA dilator muscles is reduced. The autonomic contribution to maintaining a patent airway is therefore substantial. Accordingly, diabetes could increase the risk of developing OSA via two mechanisms; by inflammation and by impairment of the autonomic nervous system controlling the UA dilator muscles. As well as being a risk factor for OSA, visceral obesity plays an important role in the development of T2DM by mobilizing free fatty acids and inflammatory cytokines, both of which promote insulin resistance [44].

**Strengths and limitations**

The strengths of the present study include the relatively high number of extremely obese subjects with a high prevalence of abnormal glucose tolerance and OSA, thereby combining three profoundly intercorrelated medical conditions. The method used to categorise sleep apnea has been validated in several studies. There are some limitations to this study, the main being the cross-

---

**Table 4 Odds of obstructive sleep apnea (AHI cut off 5) in extremely obese subjects with type 2-diabetes or prediabetes**

<table>
<thead>
<tr>
<th></th>
<th>Model 1 (OR 95% CI)</th>
<th>Model 2 (OR 95% CI)</th>
<th>Model 3 (OR 95% CI)</th>
<th>Model 4 (OR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediabetes</td>
<td>4.4 (1.9-10.6) a</td>
<td>3.3 (1.1-9.4) a</td>
<td>3.2 (1.0-10.1) a</td>
<td>4.0 (1.2-13.2) a</td>
</tr>
<tr>
<td>Type 2-diabetes</td>
<td>6.9 (2.5-18.7) a</td>
<td>4.3 (1.3-14.7) c</td>
<td>4.3 (1.2-16.4) c</td>
<td>5.4 (1.3-21.5) c</td>
</tr>
<tr>
<td>Gender</td>
<td>5.3 (1.7-17.1) b</td>
<td>5.0 (1.5-16.5) b</td>
<td>4.2 (1.2-14.4) c</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.15 (1.08-1.21) a</td>
<td>1.15 (1.08-1.22) a</td>
<td>1.15 (1.08-1.21) a</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.05 (0.97-1.14)</td>
<td>1.05 (0.97-1.14)</td>
<td>1.08 (0.99-1.18)</td>
<td>0.9 (0.7-1.3)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td></td>
<td>0.9 (0.7-1.3)</td>
<td>0.9 (0.7-1.0)</td>
</tr>
<tr>
<td>hsCRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p ≤ 0.001  b p ≤ 0.01  c p < 0.05

Data are given as odds ratio (95% CI) using multiple logistic regression analysis.
sectional study design which eliminates the ability to determine causality. The study includes mainly Caucasians, and as such the findings might not be generalizable to other populations. Our subjects are extremely obese and our results are therefore not directly applicable to less obese or normal weight subjects.

Finally, portable unattended sleep polygraphy was used to give sleep registrations: when compared to full polysomnography this monitor does not give information about sleep stages and thus cannot differentiate between REM and NREM OSA. Exact sleep time was thus not registered through an EEG, and time in bed was used to estimate sleep time.

Conclusion/clinical implications

In the present study we have shown that preDM and T2DM are commonly observed and associated with OSA in extremely obese subjects. Our findings support the recommendations from the International Diabetes Federation (IDF) suggesting that subjects with T2DM should be screened for OSA [7]. If the relationship between preDM and OSA is verified by others, this may indicate that obese subjects with preDM should also be screened for OSA.

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Authors' contributions

JMF contributed with acquisition of data, statistical analysis and interpretation of data, drafted the manuscript and revised it critically in terms of academic content. KMV contributed to acquisition of data and revised the manuscript critically in terms of academic content. JH contributed to the conception and design, interpretation of data, was involved in drafting the manuscript and revised it critically in terms of academic content. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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