Obstructive Sleep Apnea in Community-Dwelling Adults

A Clinical-Epidemiological Study

Akershus Sleep Apnea Project (ASAP)

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The chronically stressed individual
goes through three stages:
Alarm
Resistance
And exhaustion

(Dabney M. Ewin 2009)

#

With profound love to:
Elisabeth
Halvard
Håkon
Eirik

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Preface

The relation between symptoms and objective measures of disease severity has fascinated me since medical school. I therefore as a first year medical student tried to convince the dean of the Faculty of Medicine at the University of Bergen to conduct more research on the subject. I do not know the result of this talk, but personally I postponed clinical specialization when I was offered a PhD grant concerning psychosomatic aspects of obstructive sleep apnea (OSA).

In close dialogue with my main supervisor, associate professor Toril Dammen, my co-supervisor, Professor Inger Hilde Nordhus and Professor Knut Stavem I wrote a research protocol titled "psychosomatic aspects of obstructive sleep apnea syndrome". Research questions formulated addressed relations between perceived symptoms, psychiatric disorders, neuropsychological tests and objective measures of OSA. In addition I wanted to assess properties of standardized, self-reporting questionnaires in a community-based sample consisting of participants with high risk for OSA. Finally, I described aims of studying aspects of health related quality of life, illness perception and perceived sleep quality in all participants of the Akershus Sleep Apnea Project (ASAP). However, because the appointed author of the reference article of the ASAP withdrew, I was requested to write this article. Thus, this thesis address more epidemiological aspects of OSA than initially planned but unfortunately less health related quality of life, illness behavior and perceived sleep quality.

When I now, almost seven years later, conclude this phase of my life, I am urged to acknowledge my wife and children for their support and endurance. I am also grateful for the opportunity to learn from my fantastic supervisor, Toril Dammen, my co-supervisor professor Inger Hilde Nordhus, Professor Torbjørn Omland and Professor Torbjørn Moum. In addition to persons acknowledged alphabetically below, I will in particular emphasize the close and vital collaboration with my fellow PhD-students, Gunnar Einvik, Anna Randby and Silje Kjeka Namtvedt. I will also in particular acknowledge Professor Kari Kværner who initiated the project and Professor Michael Bjørn Russell, Professor Pål Guldbrandsen, Professor Kari Almendingen and Harriet Akre who all intervened in critical times. A final acknowledgement goes to all participants included in the ASAP and to other PhD-students, senior researchers, research nurses and administrative staff at the Department of Behavioral Sciences in Medicine at the University of Oslo and at Akershus University Hospital that have been involved in the project.

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The University of Oslo in general for financial support. The Institute for Clinical Research, Campus Akershus University Hospital and the Institute of Basic Medical Sciences, Department of Behavioral Sciences in Medicine for administrative support.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea Hypopnea Index
ASAP	Akershus Sleep Apnea Project
BDI	Beck Depression Inventory
BMI	Body mass index
BQ	Berlin Questionnaire
CPAP	Continuos Positive Airway Pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition).
EDS	Excessive daytime sleepiness (as identified by the ESS defined below)
ESS	Epworth sleepiness scale
ICSD-2	International Classification of Sleep Disorders, second edition
MDD	Major depressive disorder
OSA	Obstructive sleep apnea
PSG	Polysomnography
RAVLT	Rey Auditory Verbal Learning Test
SCID-I	Structured clinical interview for the DSM-IV, axis I-disorders

Summary

Background: The cardinal symptoms of Obstructive sleep apnea (OSA) are snoring or gasping while sleeping and sleepiness or fatigue while awake. In addition, OSA is associated with obesity and hypertension. Accordingly, several screening questionnaires based on self-reported symptoms, obesity and/or hypertension have been developed. Among these, the Berlin Questionnaire (BQ) was most thoroughly validated when planning this thesis. However, no study of the properties of the BQ or other screening questionnaire for OSA had been conducted in a community-based setting. Furthermore, neither the overall prevalence of OSA nor gender specific prevalences of OSA had previously been estimated in a Norwegian general population sample.

In addition to cardinal symptoms, obesity and hypertension, OSA has been associated with impaired cognitive function, anxiety, somatoform pain and depression in numerous clinical studies. However, associations observed in clinical populations can be related to the patophysiology of the target disorder, to health seeking behavior of the sub-population seeking treatment as well as to local referral practice. Thus, associations between impaired cognitive function, anxiety, somatoform pain, depression and OSA should also be studied in community-based samples consisting of persons previously not seeking- or being referred to treatment for OSA.

Community-based studies prior to this thesis have supported patophysiological relations between OSA, snoring, hypertension and obesity. On the other hand, previous community-based studies of associations between OSA and cognitive impairments or symptoms of psychiatric disorders either suffered from methodological limitations such as self-report of psychiatric symptoms, self-report of OSA/lack of respiratory variables or they reported inconsistent results. Thus, more studies conducted in community-based samples that assess respiratory variables and properly diagnosed co-morbid disorders were warranted. Furthermore, levels of neurocognitive function and prevalences of psychiatric disorders in a community-based BQ high risk sample were not known. Thus the aims of this thesis are:
Paper I:

- To evaluate screening properties of the BQ in a Norwegian, general population based sample
- To estimate overall, age and gender specific prevalences of OSA in a Norwegian general population based sample using polysomnography with

cutoff values of 5 and 15 on the apnea hypopnea index (AHI) as reference standards.

Paper II:

- To characterize cognitive function in a community-based high risk population for OSA.
- To investigate associations between verbal memory, executive function and OSA severity as assessed by the AHI, indicators of oxygen saturation and the arousal index before and after adjustment for putative confounders such as age, gender, co-morbid conditions (alcohol abuse, asthma), use of hypnosedatives, sleepiness, smoking and educational level.

Paper III:

- To estimate the prevalence of current psychiatric disorders in community-dwelling adults at a high risk for OSA, as identified by the BQ.
- To explore associations between OSA and current psychiatric disorders unadjusted and adjusted for putative confounders (demographic factors (age, sex, higher education and co-habitation) or established predictors for OSA as assessed by the BQ.

Material and methods: The source population of this thesis is the participants in the Akershus Sleep Apnea Project. The BQ was distributed to 30,000 community-dwelling adults aged 30-65 years by mail in February 2006. The clinical data in the ASAP was collected from 535 respondents of the BQ that agreed to undergo a comprehensive medical examination with overnight, in-hospital polysomnography in the period between June 2006 and January 2008. The scoring manual for the BQ defines high risk for OSA as any combination of daytime somnolence, snoring and hypertension or obesity. Thus, community-dwelling adults with high risk of OSA in this thesis all have combinations of two or three of these symptom categories. Paper II and III are based on a sub sample of 290 consecutively included BQ high risk participants. The median AHI in this clinical sample was 7.7 (25^{th} percentile 2.4, 75^{th} percentile 22.2). In addition, paper III comprises an auxiliary sample consisting of all 157 age and gender stratified BQ low risk participants included in the ASAP.

Verbal memory was assessed by the Rey Auditory Learning Test (RAVLT) and Executive function was assessed by the Stroop test. Psychiatric disorders were diagnosed with the structured clinical interview for axis I disorders (SCID-I) according to the Diagnostic and

Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Symptoms of depression were assessed by the Beck Depression Inventory (BDI).

Results: Results are presented in three papers. The main findings of the first paper were that one out of four middle-aged Norwegians were classified to be at risk of having OSA. However, the diagnostic properties of the questionnaire were sub-optimal when used as a screening tool for OSA in the general population. The prevalence estimates of OSA in a Norwegian general population were in line with almost 20 years old US estimates.

The main finding of paper II was that persons with high risk for OSA had cognitive test scores similar to persons 20-30 years older in normative samples. Mean cognitive scores of both verbal memory and executive function declined significantly when categorized by tertiles of OSA severity as assessed by the AHI, nadir oxygen saturation, mean oxygen saturation, the oxygen desaturation index and percentage time below 90% oxygen saturation in unadjusted analyses. The arousal index was not related to any cognitive test scores. After adjusting for putative confounders, only mean oxygen saturation during sleep remained independently associated with the RAVLT scores.

The main finding of paper III was that major depressive disorder, current anxiety and somatoform pain disorder were diagnosed in 12.4%, 14.8% and 19.3% of participants, respectively. At least one psychiatric disorder was diagnosed in 110 (37.9%) participants. Prevalences of psychiatric disorders did not differ significantly between high risk participants with and without OSA. The odds ratio of participants with OSA for having a psychiatric disorder compared with participants without was 0.54 (95% CI = 0.33–0.88). However, a negative association did not persist in the auxiliary sample.

Conclusions: The BQ had sub-optimal screening properties for OSA when distributed by mail to a general population sample. Moreover, estimated prevalences of OSA were comparable to more than 20 year old US estimates. Furthermore, the findings of mild impaired cognitive function and the findings that high prevalences of psychiatric disorders within a community based high risk population are novel in the OSA literature.

Regarding associations between OSA, cognitive function and psychiatric disorders, the independent positive relation found between average oxygen saturation and verbal memory strengthens and extends previous findings from clinical samples. However, previous findings of associations between OSA and anxiety or depression could not be reproduced in our study.

List of papers

I

A Norwegian Population-based Study on the Risk and Prevalence of Obstructive Sleep Apnea

J Sleep Res. 2011 Mar;20(1 Pt 2):162-70.

Harald Hrubos-Strøm, Anna Randby, Silje K Namtvedt, Håvard A Kristiansen, Gunnar Einvik, Jūratė Šaltytė Benth, Virend K Somers, Inger H Nordhus, Michael B Russell, Toril Dammen, Torbjørn Omland, Kari J Kværner

II

Obstructive sleep apnea, verbal memory and executive function in community-dwelling high-risk adults

Sleep Breath. 2012 Mar;16(1):223-31.

Harald Hrubos-Strøm, Inger H. Nordhus, Gunnar Einvik, Anna Randby,Torbjørn Omland, Kjetil Sundet, Torbjørn Moum, Toril Dammen

III

Sleep apnoea, anxiety, depression and somatoform pain: A community-based high risk sample

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Harald Hrubos-Strøm, Gunnar Einvik, Inger Hilde Nordhus, Anna Randby, Ståle Pallesen, Torbjørn Moum, Torbjørn Omland, Toril Dammen.

1.0.0 Background

1.1.0 The patient with obstructive sleep apnea

1.1.1 History

In Charles Dickens first novel, "The Pickwick Papers", the servant "Joe" is initially described as: "a fat and red-faced boy, in a state of somnolency" (Dickens 1836). The boy's state of somnolence is further portrayed: "The fat boy rose, opened his eyes, swallowed the huge piece of pie he had been in the act of masticating when he last fell asleep, and slowly obeyed his master's orders".

"The Pickwick syndrome" was introduced as a clinical syndrome by Sir William Osler in 1918. The syndrome originally included obesity, hypersomnolence, periodic breathing with hypoventilation and cor pulmonale (Guilleminault *et al.* 1976). The name of the syndrome was inspired by Dickens description of the fat boy Joe. In 1965, Gastaut, Tassinari and Duron introduced sleep studies in the research on sleep related breathing and Pickwick syndrome (Guilleminault *et al.* 1976). After this shift of focus, new pathological mechanisms were identified. One of these mechanisms was mechanical obstruction of the upper airways during inspiration. After a consensus conference in 1972, the term "obstructive sleep apnea syndrome" was introduced by Guilleminault, Tilkian and Dement (Guilleminault *et al.* 1976). The introduction of obstructive sleep apnea syndrome thus opened for a more nuanced understanding of sleep disordered breathing beyond the original "Pickwick syndrome".

1.1.2 Diagnosis of obstructive sleep apnea (OSA)

In the International Classification of Sleep Disorders, second edition (ICSD-2) (American Academy of Sleep Medicine 2005), the terminology OSA "syndrome" was abandoned. The other major change in the ICSD-2 compared to previous diagnostic requirements for OSA was that daytime symptoms were not required for a diagnosis of OSA in persons with an apnea hypopnea index (AHI) of 15 or more. The ICSD-2 diagnostic criteria for OSA are listed in Table 1.

Table 1. International Classification of Sleep Disorders, second edition. Diagnostic criteria of OSA

A, B, and D or C and D satisfy the criteria:

A: At least one of the following applies:

- The patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia
- The patient wakes with breath holding, gasping, or choking
- The bed partner reports loud snoring, breathing interruptions, or both during the patient's sleep

B: Polysomnographic recording shows the following:

- Five or more scoreable respiratory events (i.e., apneas, hypopneas, or respiratory related arousals) per hour of sleep
- Evidence of respiratory effort during all or a portion of each respiratory event (In the case of a respiratory related arousal, this is best seen with the use of esophageal manometry)

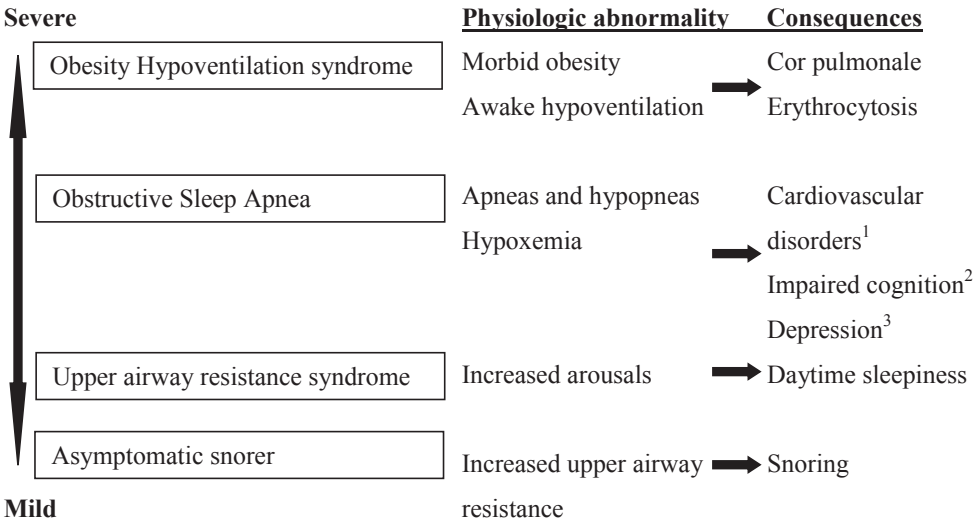
C: Polysomnographic recording shows the following:

- Fifteen or more scoreable respiratory events (i.e., apneas, hypopneas, or respiratory related arousals)
- Evidence of respiratory effort during all or a portion of each respiratory event (In the case of a respiratory related arousal, this is best seen with the use of esophageal manometry)

D: The disorder is not better explained by another current sleep disorder, medical or neurological disorder medication use, or substance use disorder.

Readers of the current literature will also encounter the term "sleep disordered breathing" which is not mentioned in the ICSD-2. Instead, the term "sleep related breathing disorders" is described, which is a broader definition than OSA also comprising central sleep apnea, obesity hypoventilation (former "Pickwick syndrome") and upper airway resistance syndrome (American Academy of Sleep Medicine 2005). The spectrum of sleep related breathing disorders is illustrated in Figure 1 (modified from (Banno and Kryger 2007)).

Figure 1: The spectrum of sleep related breathing disorders (adapted and modified from Banno and Kryger.)



1-3 = Modifications from the original figure. (1=(Somers *et al.* 2008), 2 =(Aloia *et al.* 2004), 3= (Harris *et al.* 2009))

Blood samples and respiratory effort related arousals necessary to diagnose obesity hypoventilation (Pickwick) syndrome and upper airway resistance syndrome respectively are usually not registered in routine clinical practice.

1.1.3 OSA severity

Also within OSA, there is a severity spectrum based on objective findings and symptom report. Objective findings have traditionally been categorized as mild OSA (AHI 5-15), moderate OSA (AHI 15-30) and severe OSA (AHI >30) (American Academy of Sleep Medicine 1999). However, because the length of apneas and hypopneas are mediated by complex regulation involving anatomy, ventilatory stability, end expiratory lung volume, arousal threshold and upper airway muscle control (Saboisky *et al.* 2009;White 2005), also variables assessing oxygen saturation and number of arousals are of value when categorizing objective findings. Subjective symptom report in OSA is discussed in detail below.

1.1.4 Treatment of patients with OSA

In the 1970's the treatment of choice for OSA was tracheotomy. Thus, because of the severe side effects of this treatment, most patients treated probably had severe OSA defined both by the AHI and symptom report (Guilleminault *et al.* 1976). Now, 40 years later, patients with considerably less severe OSA are treated with less invasive methods. The treatments of choice are lifestyle modification (Shneerson and Wright 2001) followed by continuous positive airway pressure (CPAP) treatment during sleep (Giles *et al.* 2006;White *et al.* 2001). However, compliance with CPAP treatment is often poor, with up to 70% of patients quitting treatment (Lindberg *et al.* 2006). Therefore, oral devices (Lim *et al.* 2004) or surgery (Bridgman *et al.* 1998) often are considered in addition to or instead of CPAP.

The main reasons for treating patients with OSA are relief of daytime symptoms and reduction of risk for traffic accidents (Krieger *et al.* 2002), cardiovascular disease (Yaggi *et al.* 2005) and death (Punjabi *et al.* 2009;Young *et al.* 2008). However, daytime symptoms in some patients remain after treatment (Giles *et al.* 2006;White *et al.* 2001). Moreover, reduction of risk for hypertension has been reported to occur only in symptomatic OSA (Kapur *et al.* 2008). Thus, clinicians identifying and treating OSA need a broad understanding of the interplay between daytime symptoms, OSA severity and co-morbid disorders. This thesis aims to expand knowledge of this interplay in a community-based sample.

1.2.0 Epidemiology and OSA

In 1946 Joseph Berkson asserted: "Various circumstances, such as the severity of the symptoms, the amenability for the disease to treatment by a local physician or the reputation of a particular hospital for treatment of particular diseases will determine the probability that a specific disease will bring its victim to a particular hospital" (Berkson 1946). Berksons statement, which is known as Berksons Bias, implies that relations between any disorder and symptoms observed in a clinical population can both be related to the patophysiology of the disorder and to features related to behavior of the sub-population seeking treatment and those who refer for treatment.

Regarding OSA, these "various circumstances" can be perception of symptoms such as daytime sleepiness or fatigue and observations of apneas or hypopneas during sleep from bed partners. Thus, in addition to the utility of evaluating screening instruments for OSA and estimating the prevalence of OSA in the general population, epidemiological-clinical studies are suitable for assessing relations initially observed in clinical samples when these "various

circumstances" are not present. Therefore, the replication of clinically observed relations in community-based samples strengthens the probability of a true relation.

1.2.1 Screening for OSA

A brief, fast track publication in 1997 resulted in a massive focus on screening for OSA (Young *et al.* 1997). Terry Young and colleagues estimated that 93% of women and 82% of men with moderate to severe OSA in the general population were undiagnosed (Young *et al.* 1997). This finding contributed to a rapid growth in clinical recognition of OSA among previously undiagnosed persons worldwide (Kapur *et al.* 2002;Young 2009). Clinical recognition of OSA is important because with proper treatment, the risk for traffic accidents (Krieger *et al.* 2002), cardiovascular disease (Yaggi *et al.* 2005) and death (Punjabi *et al.* 2009;Young *et al.* 2008) has been shown to decrease.

Several questionnaires have been developed in order to identify persons at risk for OSA (Harding 2001;Pang and Terris 2006;Rowley *et al.* 2000). Such questionnaires evaluate the risk for OSA based on self-report of symptoms and/ or features of OSA. High risk for OSA based on these questionnaires has often been used as a substitute for a diagnosis of OSA in community-based studies (Harding 2001). However, none of these questionnaires had been validated in a general population based sample prior to the planning of this thesis.

After reviewing the literature, the Berlin Questionnaire (BQ) (Netzer *et al.* 1999) was identified as the most promising questionnaire when screening for OSA in the general population. The BQ was developed based on consensus, was in frequent clinical use, and had been used to assess the risk of OSA in several clinical and non-clinical samples (Gassino *et al.* 2005;Moreno *et al.* 2004;Mustafa *et al.* 2005;Principe-Rodriguez *et al.* 2005;Singh *et al.* 2005). In addition, by 2005 the BQ was the only screening instrument for OSA that had been validated in both a general practice and a hospital setting (Gami *et al.* 2004;Netzer *et al.* 1999). Screening properties of the BQ across various samples are displayed in Table 2. I have identified 9 studies of BQ properties that have been published after the planning of this thesis (Ahmadi *et al.* 2008;Chung *et al.* 2008;Gantner *et al.* 2010;Gus *et al.* 2008;Sert Kuniyoshi *et al.* 2011;Sharma *et al.* 2006;Thurtell *et al.* 2011;Vaz *et al.* 2011;Weinreich *et al.* 2006).

Table 2: Studies of screening properties of the Berlin Questionnaire

Author	Year	Setting	Sensi-tivity	Speci-ficity	Diagnostic criteria
Netzer, N.C.	1999	General practice	0.86	0.77	AHI >5
Gami, A.S.	2004	Cardiology outpatient	0.86	0.89	AASM 1999
Studies published after the planning of this study					
Sharma, S.K.	2006	Unclear	0.86	0.95	AHI ≥5
Weinreich, G.	2006	Pulmonology rehablilitation	0.63	0.54	AHI >10
Gus, M.	2008	Cardiology outpatient	0.86	0.65	AHI ≥10
Chung, F	2008	Surgical	0.69	0.56	AHI >5
Ahmadi, N.	2008	Sleep clinic	0.68	0.49	AHI >5
Gantner, D	2010	General population with high cardiovascular risk	0.89	0.35	AHI ≥15
Vaz, A.P.	2011	Sleep clinic	0.72	0.50	AHI >5
Thurtell, MJ	2011	Ophtalmology clinic	0.83	0.58	AHI ≥5
Kuniyoshi, FH	2011	MI survivors	0.68	0.34	AHI ≥5

AASM 1999 = American Academy of Sleep Medicine report from 1999 with suggested diagnostic criteria for OSA that later have been incorporated in the International Classification of Sleep Disorders, second edition reported in Table 1. MI = Myocardial Infarction

The BQ identifies risk of OSA based on self-reported snoring, daytime somnolence and established obesity/ hypertension. General population prevalence estimates of these symptoms and/ or features of OSA had been published prior to the planning of this thesis: Regular snoring was reported to occur in 40% of the UK adult population while self-reported apneas occurred in 3.8% (Ohayon *et al.* 1997). In Denmark, habitual snoring has been reported to occur in 19.1% of adult males and 7.9% of adult females (Jennum and Sjol 1993). Norwegian prevalence estimates for snoring and self- reported apneas could not be identified. In Norway, obesity (Body mass index (BMI) > 30 kg m^{-2}) was estimated to be present in 23% of adults > 16 years of age in 2002 (www.ssb.no). Self-reported hypertension had been reported in 11,7% of respondents in a large, Norwegian community-based study (Hallan *et al.* 2003). Regarding daytime symptoms of OSA, excessive daytime sleepiness (EDS) defined by

a cut-off on the Epworth Sleepiness Scale (ESS) of more than 10 had been estimated to affect 5.9% of the Australian general adult population (Johns 1991). Norwegian general population estimates of EDS were not identified prior to the planning of this thesis.

The main quality measures of a screening instrument are sensitivity and specificity which are measures of the proportions of "true positive" and "true negative" cases respectively (Knottnerus J.A 2002). The ideal screening instrument thus has both sensitivity and specificity of 100%. However, because no screening instrument is ideal and because prevalence of the features used for screening vary between source populations, there will always be screening positive subjects without the target disorder (false positive) and screening negative subjects with the target disorder (false negative) (Knottnerus J.A 2002). On the other hand, I have not identified specific minimum criteria of a screening instrument for OSA. However, it is recommended that prediction models for OSA should have high sensitivity so as not to miss true positives, while a low specificity is rather typical and less problematic (Harding 2001).

1.2.2 Prevalence estimates and incidence of OSA

The first large- scale community-based studies of OSA were published in the late 1980's and the 1990's (Bearpark *et al.* 1995;Bixler *et al.* 1998;Bixler *et al.* 2001;Duran *et al.* 2001;Gislason *et al.* 1988;Jennum and Sjol 1992;Young *et al.* 1993). The most commonly cited prevalence estimate of OSA in the general population, defined as the occurrence of five or more apneas or hypopneas per hour, was 24% in males and 9% in females recruited from a US working population (Young *et al.* 1993). When OSA was defined as AHI $\geq$ 5 and daytime sleepiness (Criterion A and B, table 1), the prevalence was estimated to be 2% for females and 4% for males (Young *et al.* 1993). Thus, methodological differences in characterizing OSA have impact on the prevalence estimates. Moreover, gender, age, obesity, smoking, alcohol and ethnicity are all factors that influence the prevalence of OSA (Lindberg and Gislason 2000).

In Scandinavia, a Swedish study from 1989 estimated a prevalence of OSA (defined by sleepiness and AHI $\geq$ 5) of 1.3% in males which is considerably lower than the later US estimates (Gislason *et al.* 1988). A Danish study from 1992 estimated a prevalence of 10.9% for males and 6.3% for females when OSA was defined by AHI $\geq$ 5 (Jennum and Sjol 1992). When hypersomnia was added to these criteria, the estimates were 0.9% for females and 1.9% for males. Prevalence estimates of OSA in this age group from northern Europe after 1992 had not been identified when this thesis was planned. Neither the total prevalence nor age-

and sex specific prevalences for OSA have previously been estimated in a Norwegian general population based sample.

The 5-year incidence of OSA has been estimated to be 7.5% for moderately severe OSA and 16% for mild to moderate OSA (Tishler *et al.* 2003). Disease progression over time has also been reported in a Swedish cohort (Lindberg *et al.* 1999).

1.2.3 A clinical-epidemiological approach to clinically suggested associations

Prior to the planning of this thesis, most community-based studies of relations between OSA and cardinal symptoms (snoring and daytime sleepiness) had supported a causal relation between self-reported snoring or gasping and OSA (Bearpark *et al.* 1995;Young *et al.* 2002b). On the other hand, the theroretical concept of sleepiness is complex and disputed (Cluydts *et al.* 2002). A community-based study published in 2005 also reported that depression was the most significant risk factor for EDS followed by body mass index, age, typical sleep duration, diabetes, smoking, and finally OSA (Bixler *et al.* 2005).

In addition to cardinal symptoms, community-based studies of relations between OSA and obesity, hypertension, and cardiovascular morbidity also had supported previous findings of positive associations prior to this thesis (Young *et al.* 2002a). However, community-based studies of relations with neurocognitive impairment (Berry *et al.* 1987;Boland *et al.* 2002;Hayward *et al.* 1992;Kim *et al.* 1997;Telakivi *et al.* 1988) and symptoms of psychiatric disorders (Enright *et al.* 1996;Kripke *et al.* 1997;Ohayon 2003) either suffered from methodological limitations or reported inconsistent findings. It was therefore decided to specifically focus on cognitive function and co-morbid psychiatric disorders in this study.

OSA and cognitive function

Neurocognitive function consists of basal processes (i.e. attention, motor speed and vigilance) and more differentiated cognitive functions, of which impairments in verbal memory (Naegele *et al.* 2006;Twigg *et al.* 2010) and executive function (Verstraeten *et al.* 2004) have been found to be most strongly related to OSA. Prior to the planning of this thesis, studies based on clinical samples had indicated an association between moderate to severe OSA and impaired cognitive function (Aloia *et al.* 2004;Beebe *et al.* 2003;Decary *et al.* 2000;Engleman and Joffe 1999;Verstraeten and Cluydts 2004). I identified five community-based studies (Berry *et al.* 1987;Boland *et al.* 2002;Hayward *et al.* 1992;Kim *et al.* 1997;Telakivi *et al.* 1988) and two studies of mild OSA in volunteers (Adams *et al.* 2001;Redline *et al.* 1997) that had assessed cognitive function with rater-administered instruments in addition to objective

sleep measures prior to this thesis. I also identified a Scandinavian community-based study that assessed cognitive function by self-report (Jennum and Sjol 1994). Three of the identified studies reported analyses by variables assessing oxygen saturation (4% oxygen desaturation index, lowest oxygen saturation or percentage time below 90% oxygen saturation (Adams *et al.* 2001;Boland *et al.* 2002;Telakivi *et al.* 1988)). In these studies, the associations with oxygen saturation were at least as strong as the associations reported between cognitive functions and measures of apneas and hypopneas. Accordingly, there was a need for further studies of the relations between cognitive function and OSA severity as assessed by the AHI, indicators of oxygen saturation and the arousal index.

Affected cognitive domains in previous community-based studies are verbal memory (Wechsler Memory Scale (Telakivi *et al.* 1988), declarative memory factor (Adams *et al.* 2001)), working memory (composite factor (Adams *et al.* 2001)), spatial orientation (Clock Test (Telakivi *et al.* 1988)), executive function (Wechsler Adult Intelligence Scale-Revised Digits Backward Subtest (Redline *et al.* 1997)) and cerebral efficiency (composite factor (Hayward *et al.* 1992)).

Finally, previous community based studies have only to a minor extent been able to control for putative confounders of the relation between cognitive impairment and OSA, such as sociodemography, alcohol abuse, sleepiness, use of hypnosedatives, smoking and asthma (Adams *et al.* 2001;Boland *et al.* 2002;Kim *et al.* 1997;Redline *et al.* 1997). Because such factors are likely to be related both to cognitive function and to OSA, control of such putative confounders are warranted in community-based studies of this relation (Saunamaki and Jehkonen 2007a).

OSA and psychiatric disorders

In several studies of clinical populations, OSA has been linked to symptoms of psychiatric disorders such as depression, mania, anxiety, psychosis, hypochondriasis and somatization (Aikens and Mendelson 1999;Bardwell *et al.* 1999;Kales *et al.* 1985;Sharafkhaneh *et al.* 2005). However, as explained above, such associations may be overestimated in clinical samples because of selection to hospitals by “various circumstances” (Berkson 1946). Thus, regarding OSA, persons who experience daytime sleepiness or fatigue and persons with spouses that observe apneas or hypopneas during sleep will presumably be more likely to seek help and thus be referred to OSA evaluation than others. The effect of such selection presumably leads to a higher proportion of undiagnosed OSA among persons without daytime symptoms or living alone. It was reported prior to the planning of this thesis that daytime

sleepiness is more strongly related to depression than to OSA (Bixler *et al.* 2005). Moreover, the effect of shared risk factors had been postulated to affect the relation between depression and OSA (Andrews and Oei 2004). The effect of shared risk factors thus is a limitation to studies of this relation when one relies on self-reports of previously diagnosed OSA. For example, Ohayon's findings from 2003 (Ohayon 2003), where 17.6% of adults in the general population with self-reported OSA in a telephone interview were diagnosed with co-morbid depression, could have been affected by such selection. A community-based study that assessed both OSA and psychiatric disorders with proper diagnostic tools was therefore warranted (Saunamaki and Jehkonen 2007b).

The general prevalence of major depressive disorder in the Norwegian general population has been estimated to be 7.3% (Kringlen *et al.* 2001). The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for major depressive disorder (MDD) are displayed in appendix 1.

In addition to the abovementioned study by Ohayon, we identified two other community-based studies of the relation between OSA and depression (Enright *et al.* 1996;Kripke *et al.* 1997). The study by Kripke et al. reported no relation (Kripke *et al.* 1997) and the study by Enright et al reported a gender- specific relation (i.e. an association among women) (Enright *et al.* 1996). Both studies relied on self-report of symptoms of depression while the study by Ohayon diagnosed depression and psychotic symptoms by interview (Ohayon 2003). No community-based study was identified that had assessed the relationship between OSA and symptoms of other psychiatric disorders. Community-based studies assessing depression both by interview and with self-report were therefore also warranted.

Anxiety disorders as a whole are the largest diagnostic group in the general European population (Wittchen and Jacobi 2005). The diagnostic criteria of anxiety disorders are displayed in appendix 2. The second largest group of psychiatric disorders in the European general population is somatoform disorders with estimated prevalences of 1.1-11% (Wittchen and Jacobi 2005). DSM-IV descriptions of hypochondriasis, somatoform pain disorder and somatization disorder are displayed in appendix 3. The point prevalence of any psychiatric disorder defined by the DSM-III-R criteria has been estimated to be 32.8% in Norway (Kringlen *et al.* 2001) and 27% in the general, adult EU population 18-65 years of age. Despite the report of high prevalences of anxiety and somatoform disorders in the population and clinical observation of such symptoms in a high proportion of OSA patients, no previous

study have assessed the prevalence of these disorders among OSA patients or persons at risk of OSA.

In addition to the potential effect of sleepiness as a shared risk factor between OSA and psychiatric disorders, age and sex are putative confounders of all associations observed in a clinical context (Rothman 2002). Thus, studies of associations between OSA, cognitive function and psychiatric disorders should ideally be designed to control for age, sex and a selection of previously identified, putative confounders.

2.0.0 Aims of the study

Paper I:

- To evaluate screening properties of the BQ in a Norwegian, general population based sample
- To estimate overall, age and gender specific prevalences of OSA in a Norwegian general population based sample using polysomnography with cutoff values of 5 and 15 on the AHI as reference standards.

Paper II:

- To characterize cognitive function in a community-based high risk population for OSA
- To investigate associations between verbal memory, executive function and OSA severity as assessed by the AHI, indicators of oxygen saturation and the arousal index before and after adjustment for putative confounders such as age, gender, co-morbid conditions (alcohol abuse, asthma), use of hypnosedatives, sleepiness, smoking and educational level.

Paper III:

- To estimate the prevalence of current psychiatric disorders in community-dwelling adults at a high risk for OSA, as identified by the BQ.
- To explore associations between OSA and current psychiatric disorders unadjusted and adjusted for putative confounders (demographic factors (age, sex, higher education and co-habitation) or established predictors for OSA included in the BQ).

3.0.0 Material and methods

3.1.0 Design

This thesis is based on data from the Akershus Sleep Apnea Project (ASAP), a cross-sectional, two-phased epidemiological- clinical study, initiated by professor Kari J. Kværner, department of Ear- Nose and Throat, Akershus University Hospital. The cross-sectional design was applied in all three papers.

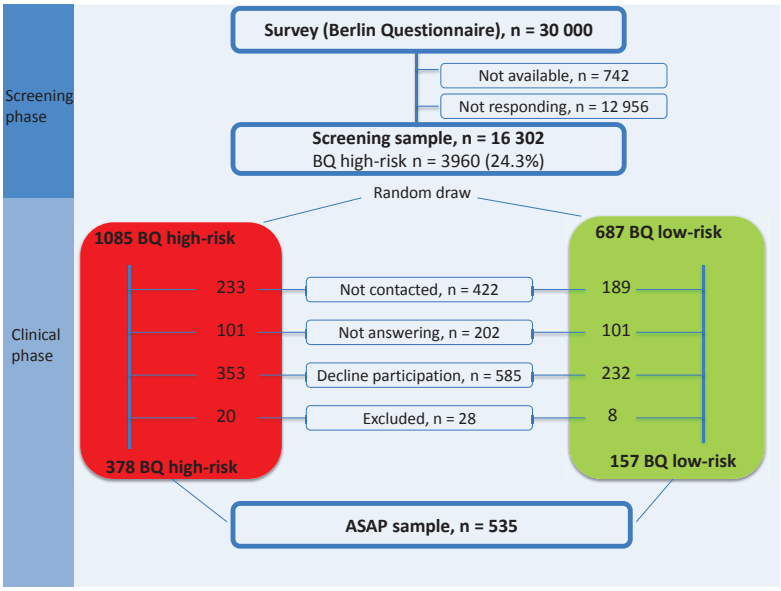
3.2.0 Material

3.2.1 Screening sample

A questionnaire and a letter describing the study were mailed twice to a sample of 30,000 age- and sex-stratified inhabitants of the eastern part of Akershus (except Asker and Bærum), western part of Hedmark (except communities north of Trysil, Åmot and Ringsaker) and southern part of Oppland counties (except Vestre Slidre, Gausdal and Øyer) in central eastern Norway. The sample consisted of fourteen strata with 2000 randomly drawn persons from the National Population Register. Each stratum was classified by sex and age. Drawn males and females were 30, 35, 40, 45, 50, 55 or 60 years of age. In addition, two strata consisting of 1000 males and 1000 females aged 65 years were randomly drawn.

Questionnaires were answered by returning the paper version or via a web-based solution. Because 742 letters were returned unopened or we got information that the drawn person was deceased or abroad, the study population consisted of 29,258 subjects. Of these, 16,302 persons responded (55.7%). Inclusion of participants to the ASAP is presented in Figure 2.

Figure 2: Inclusion of participants



BQ = Berlin Questionnaire, ASAP = Akershus Sleep Apnea Project

The response rate to the screening sample was significantly higher for persons aged 50 years and more (62.0%) than for persons below 50 years of age (50.1%) and was higher for females (59.0%) than males (52.4%). Stratified response rates are presented in appendix 4. Males aged 30 used the web-solution most (22.3%) and females aged 65 least (1.4%). Age and gender stratified analyses of differences between web and paper responses revealed no systematic differences.

Risk classification for OSA in the ASAP was based on a Norwegian translation of the BQ (Netzer *et al.* 1999). The English version of the BQ was translated into Norwegian using a standardized translation procedure. The English version was first translated to Norwegian by two native speaking Norwegian physicians who were fluent in English (Kari J. Kværner and Hilde Bergum Furuseth) and then translated back to English by two bilingual physicians (Torbjørn Omland and Gunnhild Karevold).

The scoring algorithm for the BQ defines high risk for OSA as any combination of risk categories of daytime somnolence, snoring and hypertension or obesity (Chung *et al.* 2008) (appendix 5). Thus, community-dwelling adults with high risk of OSA in this thesis all have combinations of two or three symptom categories as described in the scoring algorithm. It is also worth noting that some studies where the BQ has been administered also contain an additional question regarding frequency of falling asleep while driving (Hiestand *et al.*

2006;Kapsimalis and Kryger 2009). However, scoring of this additional question is not described in the scoring algorithm (appendix 5). Accordingly this question was not included in the screening questionnaire. Moreover, neither the reference article (Netzer *et al.* 1999) nor the scoring algorithm contains instructions for the handling of missing data. Missing of one or more BQ item occurred in 43.8% of the questionnaires in the screening sample. After careful consideration, missing was recoded to "zero" to establish risk status of all respondents. The BQ low risk questionnaires with missing items (n = 5541) were made unavailable for the subsequent draws.

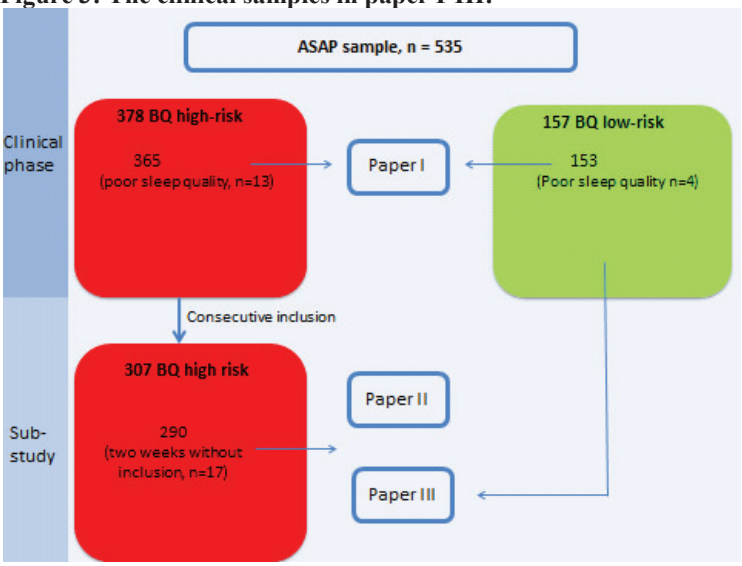
Also questionnaires received more than 4 months after the first mailing (n= 41) or without a contact telephone number (n = 729), and 672 questionnaires that were administratively misplaced were regarded as not eligible (n = 1442). In paper I, the screening sample minus these 1442 persons is labeled "the estimation sample".

3.2.2 Clinical sample paper I

Five stratified, random draws were conducted (April 06, August 06, February 07, August 07 and October 07). All draws were conducted by the project statistician, Jūratė Šaltytė Benth, in close co-operation with the project database manager, Anita Fjellum, who monitored inclusion to the clinical sample. In total, a pool of 1772 responders was randomly drawn. Among these, 1085 were BQ high risk persons sub-stratified by 242 persons oversampled with previous ear surgery, 155 persons with diabetes and 581 persons with no previous ear surgery, myocardial infarction or diabetes. Among these BQ high risk persons, also 107 responders with previous myocardial infarction were randomly drawn.

Drawn persons were invited by mail and approached by telephone. Invited persons were excluded after three unsuccessful attempts of contact (n = 202), use of continuous positive airway pressure (n = 10), pregnancy (n = 9), lack of Norwegian language skills (n = 5), or severe physical impairment (n = 4). Because of administrative failure, 6 of these persons fulfilling exclusion criteria were examined but later excluded from the clinical sample. A total of 585 persons declined the invitation and 422 drawn persons were never invited, leaving a total clinical sample of 535 persons included in the overall project (378 BQ high risk persons, participation rate = 44.3%) (Figure 3). In paper I, 17 persons were excluded from analysis according to poor sleep quality (Young *et al.* 1993). The sample in paper I thus comprised of 518 persons.

Figure 3: The clinical samples in paper I-III:



ASAP = Akershus Sleep Apnea Project, BQ = Berlin Questionnaire

3.2.3 Clinical sample paper II and III

Figure 3 also illustrates inclusion to the psychosomatic sub-study which is based on clinical examinations of the 290 first, BQ high risk participants of the ASAP between June 2006 and March 2007. In paper III, also auxiliary analyses from ASAP controls were provided. All participants in the psychosomatic sub-study underwent comprehensive psychiatric and neuropsychological testing in addition to diagnostic procedures applied to all persons included in the ASAP.

The choice to assess 290 BQ high risk participants in the psychosomatic sub-study was based on an expected OSA prevalence of 50% among BQ high risk participants (Netzer *et al.* 1999). The prevalence of MDD among BQ high risk participants without OSA was expected to be approximately similar to a general population prevalence of 7% (Kringlen *et al.* 2001). Because previous community-based studies of the association between OSA and MDD had reported conflicting results, we aimed to detect as small differences between the groups as possible. We thus decided to be able to detect a 50% higher proportion of MDD among participants with OSA (11%) compared to participants without OSA (7%). This difference corresponds to an effect size of 0.15. Thus, with this effect-size, 5% alpha, 80% statistical power and a one-sided test, a suggested sample size is 292 (http://www.stat.ubc.ca/~rollin/stats/ssize/b1.html).

An overview of the screening sample, the drawn sample, the ASAP sample and the clinical samples are reported in Table 3.

Table 3: Description of the samples

Screening factor	Screening sample	Drawn sample	ASAP sample	Clinical sample paper I	Clinical sample paper II-III
N	**16.302**	**1772**	**535**	**518**	**290**
Mean age (SD)	47.8 (10.7)				
High risk	48.8 (10.3)	49.1 (11.6)	48.9 (11.2)	48.6 (11.1)	48.2 (11.2)
Low risk	47.5 (10.8)	47.2 (11.8)	47.6 (11.4)	47.6 (11.4)	
Male sex (%)	7629 (46.8)				
High risk	2198 (55.5)	590 (54.4)	213 (56.3)	207 (56.7)	162 (55.9)
Low risk	5431 (44.0)	321 (46.7)	79 (50.3)	77 (50.3)	
BQ risk categories and related variables					
I: Snoring (%)	6665(40.9)				
High risk	3654 (92.3)	996 (91.8)	343 (90.7)	332 (91.0)	264 (91.0)
Low risk	3011 (24.4)	246 (35.8)**	61 (38.9)**	61 (39.9)**	
II: Somnolence (%)	4072 (25.0)				
High risk	2498 (63.1)	682 (62.9)	261 (69.0)*	255 (69.9)*	205 (70.7)*
Low risk	1574 (12.8)	76 (11.1)	19 (12.1)	18 (11.8)	
III: HT or obesity (%)	3998 (24.5)				
High risk	2624 (66.3)	745 (68.7)	252 (66.7)	240 (65.8)	193 (66.6)
Low risk	1374 (11.1)	71 (10.3)	15 (9.6)	15 (9.8)	
Mean BMI (SD)	26.0 (4.3)				
High risk	29.1 (5.2)	28.4 (5.3)*	29 (5.0)	29.0 (5.0)	29.0 (4.9)
Low risk	25.0 (3.4)	25.4 (3.4)**	25.4 (2.9)	25.4 (2.9)	
Epworth sleepiness scale	6.9 (4.0)				
High risk	8.8 (4.5)	8.9 (4.5)	9.7 (4.5)**	9.8 (4.5)**	9.8 (4.5)**
Low risk	6.3 (3.7)	6.3 (3.6)	6.5 (3.9)	6.6 (3.9)	
Daily depressive thoughts	1068 (6.7)				
High risk	593 (15.3)	170 (15.9)	47 (12.6)	44 (12.3)	37 (12.9)
Low risk	475 (4.0)	23 (3.4)	7 (4.5)	7 (4.6)	
Stratification variables					
Diabetes (%)	546 (3.4)				
High risk	274 (7.1)	155 (14.6)**	45 (12.1)**	44 (12.3)**	33 (11.6)**
Low risk	272 (2.2)	15 (2.2)	2 (1.3)	2 (1.4)	
Previous MI (%)	344 (2.1)				
High risk	150 (3.9)	136 (12.9)**	49 (13.3)**	46 (12.9)**	41 (14.5)**
Low risk	194 (1.6)	11 (1.6)	2 (1.3)	2 (1.3)	
Otitis media surgery (%)	2145 (28.5)				
High risk	634 (31.5)	283 (46.7)**	110 (51.9)**	106 (52.0)**	85 (50.6)**
Low risk	1511 (27.4)	73 (24.4)	12 (18.2)	12 (18.8)	

[a] = $p < 0.05$, ** $p < 0.01$ for differences between screening sample and each of the other samples

3.3.0 Methods:

All variables used in analyses in this thesis are presented in table 4.

Table 4: Description of variables

Strata and screening questionnaire	Description	Range[a]	Paper
Gender	Strata variable	M/F	All
Age	Strata variable	30-65	All
Berlin Questionnaire high risk	Strata variable	Yes/no	All
Berlin Questionnaire risk category I	Snoring risk category	Yes/no	All
Simple snoring	Snoring any night	Yes/no	I
Habitual snoring	Snoring every night or almost every night	Yes/no	I
Berlin Questionnaire risk category II	Daytime somnolence	Yes/no	All
Berlin Questionnaire risk category III	Body mass index >30 and/or hypertension	Yes/no	All
Body mass index	Calculated from reported height/weight	18-51	All
Obesity	Body mass index > 30	Yes/no	All
Hypertension		Yes/no	All
Self-reported previous myocardial infarction	Strata variable	Yes/no	All
Self-reported history of ear surgery	Strata variable	Yes/no	All
Self-reported diabetes	Strata variable	Yes/no	All
Epworth Sleepiness Scale (ESS)	Sum score	0-22	All
Excessive daytime sleepiness	ESS > 10	Yes/no	All
Frequent depressive thoughts or loss of interest	3-4 times per week or more	Yes/no	III
Self-reported asthma		Yes/no	II
Polysomnography			
Total sleep time	Minutes	68-639	I, III
SWS in percentage of Total sleep time	Percentage	0-62	I
Sleep latency to stage 1 sleep	Minutes	1-479	III
Wake time after sleep onset	Minutes	0-326	III
Sleep efficiency	Percentage	16-100	III
Table continued on next page			

Table 4, continued

Apnea-hypopnea index	Number of apneas and hypopneas pr hour	0-110	All
Mean O2 saturation	Average saturation during sleep	82-98	II
Arousal index	Arousals per hour	2-808	II
Nadir oxygen saturation	Lowest value	54-95	II
Percentage time below 90% saturation	Percentage	0-94	II
Neurocognitive assessment			
Stroop interference time	Seconds	9-85	II
Rey Auditory Verbal Learning test score	Words learned	18-61	II
Structured Clinical Psychiatric Interview and self-report of depression			
Various DSM-IV psychiatric disorders[b] SCID	Diagnosed disorder	Yes/no	III
Beck depression inventory	Sum score	0-41	III
Relevant standard blood tests			
Blood hemoglobin	Gram/deciliter	10-18	II
Serum ferritin	Microgram/liter	5-593	II
Demographic			
Education	College/university or higher	Yes/no	II, III
Co-habitation		Yes/no	I, III
In regular work		Yes/no	I
Smoking		Yes/no	I
Alcohol abuse	Diagnosed disorder	Yes/no	II, III

[a] = Observed range in the clinical sample
[b] = See table 2-4 for specific description

The table contains references to the articles in which the variables are described. Additional information of the variables not provided in the papers is described in the subsequent sections.

3.3.1 The screening questionnaire

In addition to the BQ (Netzer *et al.* 1999), the one page screening questionnaire (appendix 6) consisted of self-report of height and weight, the Epworth Sleepiness Scale (ESS) (Johns 1991) and 31 questions specifically requested by the supervisors of the respective sub studies of the ASAP.

Relevant for this thesis, one BQ item assessing snoring frequency was re-coded in paper I in accordance with a previous study (Partinen and Gislason 1995) with the purpose of comparing prevalences of snoring and habitual snoring with previous literature. Moreover,

body mass index (BMI) was calculated (weight (kg)/height $(m)^2$) based on self-reported height and weight in all three papers. Finally, the BQ obesity/hypertension risk category was sub-divided into a hypertension and an obesity sub-group with the purposes of comparing prevalences with previous literature and clinical measurements. Agreement (Cohen's Kappa) between self-reported BQ risk factors of obesity and hypertension in the screening questionnaire, standardized physical examination (described below) and interview of participants in the ASAP sample were compared. Cohen's Kappa scores were 0.8 for obesity and 0.7 for hypertension respectively. Mean self-reported BMI was 28.0. Measured BMI was 28.9 which was significantly different from self-reported BMI by paired samples t-test.

The ESS (Johns 1991) is a frequently used questionnaire assessing subjective sleepiness. The Norwegian translation used in this thesis has previously been used to estimate prevalence and risk factors of EDS in Norway (Pallesen *et al.* 2007). Internal consistency of the ESS as assessed by Cronbach's alpha in both the screening sample and in the clinical sample was 0.8. The test-retest reliability between the screening sample and the clinical sample was 0.7 as assessed by the Intraclass Correlation Coefficient.

Finally, in paper III, information regarding daily depressive thoughts was used in analyses assessing selection bias between the screening- and clinical samples.

3.3.2 Polysomnography (PSG)

The technical specifications of the in-hospital polysomnographic equipment used in the ASAP and clinical scoring procedures have been comprehensively described in Paper I. In addition to measures of respiratory events, oxygen saturation and arousals, various variables of sleep quality have been reported in the three papers (total sleep time, slow wave sleep in percentage of total sleep time, sleep latency, wake time after sleep onset and sleep efficiency).

Regarding the oximetry variables, inspection of summary graphs of the initially scored sleep reports revealed potential artifacts in the oximetry variables from 68 participants of the psychosomatic subsample. The scoring of oximetry variables from these participants were re-inspected by the original two scorers (Janne Grønli and Ingvild West Saxvig) and artifacts were corrected in oximetry data for 40 participants where obvious artifacts were identified.

3.3.3 Cognitive tests

Among cognitive domains previously shown to be affected in OSA, it was decided to assess verbal (declarative) memory by the Rey Auditory Verbal Test (RAVLT) (Schmidt 1996) and executive function by a shortened version of the Comali/Kaplan Stroop test (Egeland *et al.*

2003). The shortened version of the Comali/Kaplan Stroop test (Egeland *et al.* 2003) was used to assess response inhibition which is regarded a measure of executive function. Compared with other tests of executive function, the Stroop test adjusts for attention, which should optimally be controlled for when assessing executive function (Verstraeten and Cluydts 2004). General population norms have not been published for this version, and norms were calculated from an available data set (Rund *et al.* 2006).

Normative data from a meta analysis of the RAVLT was used for comparison regarding this test (Mitrushina *et al.* 2005).

The two neurocognitive tests were chosen because they were short regarded extensively validated and they were available with norms without costs through our co-operation with Professor Kjetil Sundet. Finally, both tests were listed by Decary et al. in a proposed test battery of cognitive functions related to OSA (Decary *et al.* 2000).

3.3.4 Psychiatric assessments

Diagnostic interview

Current (criteria met within the past month) psychiatric disorders were diagnosed by the structured clinical interview for DSM-IV, axis I-disorders (SCID-I) (First Michael B *et al.* 1995). The SCID-I is regarded the gold standard research tool for assessment of psychiatric disorders. Interviews were conducted by me and taped. I was trained by an experienced research psychiatrist (TD) for 9 months before the initiation of the study.

Inter-rater reliability of the interview was assessed in two ways: The first 30 interviews in the study plus another 44 cases with unclear diagnoses were analyzed separately by HHS and TD and discussed until consensus was reached. Secondly, Cohen's Kappa values for agreement between diagnoses obtained by TD and me in 40 randomly selected interviews were calculated for the following categories: MDD, somatoform pain disorder and a composite category termed "current anxiety". The latter category included participants who suffered from at least one current anxiety disorder (panic disorder with and without agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder and generalized anxiety disorder). Specific phobia was not included because the disorder was regarded as clinically less important. A composite category for anxiety was composed because of few cases with each anxiety disorder. The inter rater reliability scores for presence/absence of the selected three diagnostic categories (MDD, somatoform pain disorder and current anxiety) were excellent (Cohen's kappa = 1.0) (Landis and Koch 1977).

Self-report of depressive symptoms

Current symptoms of depression were assessed by the Beck Depression Inventory, version I (BDI) (Beck *et al.* 1961). The BDI consists of 21 items of affective, cognitive and somatic symptoms of depression, each scored 0-3 (Beck *et al.* 1961)(appendix 7). The BDI has been frequently used to assess severity of depression and was regarded best for comparisons with other studies of depression related to OSA. The internal consistency for the BDI in the ASAP sample, as assessed with Cronbach's alpha was 0.9, which is regarded excellent.

3.3.5 Fasting blood samples

Morning fasting blood samples were collected from the antecubital vein of all participants. Standard tests including blood hemoglobin and ferritin used in paper III were analyzed the same day by conventional enzyme-assays at the laboratory at Stensby Hospital.

3.3.6 Demographic variables:

Demographic data in addition to age and gender was based on information from a validated standardized questionnaire from the Cohort of Norway (Naess *et al.* 2008). Specific variables derived from these variables are described in the respective papers.

3.3.7 Clinical interview and examination:

All participants underwent a semi-structured interview where previous illness and medication use was registered. In addition, a standard clinical examination was performed, including two repeated measures of weight and height. BMI was calculated by the formula described above.

3.5.0 Ethics

The study protocol was approved in 2005 by the Regional Committee for Medical Research Ethics in eastern Norway, the National Data Inspectorate, The Norwegian Directorate of Health and the Norwegian Social Science Data Services. All participants received written information by mail. A written consent for participation was obtained before inclusion to the ASAP sample. If the examinations performed revealed signs of any disease needing attention, the person's general practitioners was informed if the participant consented.

3.6.0 Statistical analyses

3.6.1 Quality control:

Data from the screening questionnaire was manually scanned and corrected consecutively. Data from PSG reports of the clinical sample in paper II-III, neurocognitive tests and the psychiatric interview was punched manually by me into a research database. Remaining PSG data, data from standard blood samples, clinical interview and examination and self-report data from participants that were not able to answer the computerized questionnaires were punched into the database by other researchers or by a technician.

The quality of all data was thoroughly checked prior to scientific analyses by descriptive statistics assessing range and outliers. Values out of range and extreme outliers were checked against raw data and eventually corrected in the database. All corrections were logged.

3.6.2 Estimation of BQ properties and prevalences of OSA

The quality control procedures revealed that a systematical bias had occurred when including BQ low risk participants to the clinical sample. A decision to exclude BQ low risk respondents from the random draws was the mechanism of this systematical bias. Respondents that had answered “no” to the question “do you snore” were more likely to not fill in other questions regarding snoring loudness and frequency than snorers. It was decided to adjust for this bias in the same statistical model that adjusted for stratified sampling in paper I. A description of this statistical procedure is published as an online supplement to paper I (appendix 8).

3.6.3 General statistical considerations

All continuous data were tested for normality by the Kolmogorov-Smirnov test. Non-normalized variables were either log-transformed and re-checked for normality, or categorized. Comparisons between participants and non-participants were performed with Chi Square test for categorical variables and Student’s T-test /Mann Whitney U-test for normally distributed/ non-normally distributed continuous variables respectively. Bivariate correlations were assessed with Pearson’s correlation coefficient or Spearman’s rho, as appropriate. More detailed descriptions of statistical considerations and multivariate analyses are presented in each paper.

In all analyses a two-tailed p-value < 0.05 was used as cut-off for statistical significance. All statistical analyses were obtained by using the Statistical Package for Social Sciences, versions 16.0-18.0.

4.0.0 Summary of papers and results

4.1 Paper I

A Norwegian Population-based Study on the Risk and Prevalence of Obstructive Sleep Apnea

Summary

The BQ is a widely used screening tool for OSA, but its performance in a general population based sample is unknown. The prevalence of OSA in middle-aged adults is not known in Norway. Accordingly, the aims of the current study were to evaluate the utility of the BQ for OSA screening in the general population and to estimate the prevalence of OSA in Norway. The study population consisted of 29,258 subjects (aged 30–65 years, 50% female) who received the BQ by mail. Of these, 16.302 (55.7%) responded. 518 persons were included in the clinical sample and underwent in-hospital polysomnography. Screening properties and prevalence were estimated by a statistical model that adjusted for bias in the sampling procedure. Among the 16.302 respondents, 24.3% (95% CI = 23.6–25.0%) were classified by the BQ to be at high risk of having OSA. Defining OSA as an AHI ≥ 5, the positive predictive value of the BQ was estimated to be 61.3%, the negative predictive value 66.2%, the sensitivity 37.2% and the specificity 84.0%. Estimated prevalences of OSA were 16% for AHI ≥ 5 and 8% for AHI ≥ 15. In conclusion, the BQ classified one out of four middle-aged Norwegians to be at high risk of having OSA, but the screening properties of the BQ were sub optimal. The estimated prevalence of OSA was comparable to previous estimates from general populations in the US, Australia and Europe.

4.2 Paper II

Average nightly oxygen saturation, verbal memory and executive function in population-dwelling adults at high risk of having obstructive sleep apnea

Summary

Purpose: Cognitive functions in community-dwelling adults at high risk of OSA have not been described, nor are associations between cognitive functions and OSA severity fully understood. The study aimed to describe verbal memory and executive function in community-dwelling adults identified by the BQ and to investigate associations between these cognitive domains and different OSA severity indicators.

Methods: Among 29,258 age- and gender stratified persons 30–65 years who received the BQ by mail, 16,302 (55.7%) responded. From 654 randomly drawn respondents with BQ high risk who were approached for study participation, 290 participants (55.9% males, mean age 48.2 years) were included. Verbal memory was assessed by RAVLT and executive function by the Stroop test. OSA severity indicators were assessed by polysomnography.

Results: Mean (standard deviation) verbal learning score was 42.0 (8.9), mean interference time was 31.1 (12.7), median (25^{th} percentile, 75^{th} percentile) AHI was 7.7 (2.4–22.2) and mean average oxygen saturation was 94.3 (2.0). Verbal learning score was independently associated with average oxygen saturation ($\beta = 0.721$, $p = 0.025$) in multivariate linear regression models adjusted for putative confounders. Interference time was only related to OSA severity indicators in bivariate analyses.

Conclusions: Verbal memory and executive function impairments were mild in community-dwelling adults at high risk of OSA. Average oxygen saturation was the indicator of OSA severity most strongly associated with cognitive function.

4.3 Paper III

Sleep apnoea, anxiety, depression and somatoform pain: A community-based high risk sample

Summary

OSA has been associated with psychopathology. However, community-based studies that measure both psychiatric diagnoses and OSA are lacking. This study reports current psychiatric disorders in community-dwelling adults at high risk for OSA identified by the BQ. Further, associations between OSA and current psychiatric disorders, unadjusted and adjusted for putative confounders, are reported.

A sub sample of the ASAP consisting of 290 adults, 30–65 years, with positive BQ screening, underwent the SCID-I and polysomnography. Auxiliary analyses from ASAP controls are provided.

The median AHI score in the sample was 7.7 (25^{th} percentile 2.4, 75^{th} percentile 22.2). Major depressive disorder, current anxiety and somatoform pain disorder were diagnosed in 12.4%, 14.8% and 19.3% of participants, respectively. At least one psychiatric disorder was diagnosed in 110 (37.9%) participants. The odds ratio of participants with OSA for having a psychiatric disorder compared with participants without was 0.54 (95% CI = 0.33–0.88). A negative association did not persist in the auxiliary sample. Results with OSA defined by AHI ≥15 and AHI ≥30 is presented in appendix 9.

In conclusion, more than one-third of participants in a community-based, BQ high-risk sample were diagnosed with a psychiatric disorder. A negative association between OSA and psychiatric morbidity was found.

5.0.0 General discussion

5.1.0 Methodological issues

5.1.1 Design

The strength of the community-based two-phase design is that results may be generalized to the general population if properly weighted. Only the results in paper I were weighted. Hence, the results in paper II and III may be generalized to community-dwelling persons with BQ high risk. However, in paper III, also results from a BQ low risk population were provided. Finally, it must be kept in mind that the cross-sectional design of the study limits interpretation of causal relations.

5.1.2 Sample

Sample size

The size of the screening sample and the ASAP sample and the decision that 3/4 of the participants should fulfill criteria of BQ high risk status were set prior to the planning of the thesis. However, the size of the clinical sample in paper I was large enough to build a prediction model that yielded estimates of screening properties and prevalences with relatively narrow 95% confidence intervals.

Regarding the sample size calculation leading to the decision to assess cognitive function and psychiatric disorders only among BQ high risk participants, the empirical observation of significantly more psychiatric disorders among participants without OSA than with OSA were different from the assumption behind these estimates. On the other hand, the size of the clinical sample in paper II and III was sufficiently large to reject the null hypothesis of no differences in psychiatric disorders as a whole between participants with and without OSA. The effect-size of this difference was 0.31. It is, however, possible that in a larger sample, differences on the level of individual psychiatric disorders could have been found. The effect-size of the non-significant difference between MDD and OSA was 0.26. Thus, if the sample-size had been calculated with a two-sided test, rather than a one-sided test, significant differences between individual psychiatric disorders and OSA might have been found in a larger sample.

Internal validity

The discussion of internal validity has been categorized between investigator-dependent factors and participant-dependent factors.

Investigator-dependent factors

The most important investigator-dependent factor affecting the results of paper I was the handling of missing items in the BQ. No recommendations in the existing literature regarding the BQ on how to deal with this problem were found. Accordingly, a sensitivity analysis was performed to estimate the maximum impact of the potential bias introduced by our strategy of scoring missing values as zero was conducted. The analysis indicated that "most severe scoring on missing items" would increase the proportion of BQ high risk participants in the screening sample from 24.3% to 27.7%. Thus, the analysis suggested a minor effect on BQ high risk classification. However, as reported in section 3.6.2, quality control procedures revealed that contrary to the decision of scoring missing values as "zero", all BQ low risk questionnaires with missing items (n = 5541) had been made unavailable for the subsequent draws, apparently to avoid misclassification among persons recruited to the clinical part of the project. This decision, unknown for me before analyzing data, resulted in a selection of snorers to the BQ low risk group in the ASAP sample and the clinical samples. The effect of the bias can be seen among BQ low risk participants in the BQ snoring category of table 3. The most plausible mechanism of this bias is that responders who had indicated "no snoring" on the first question of the BQ snoring category were more likely to have missing values in further items than responders that reported snoring. Because snoring is an established risk factor of OSA, this bias probably contributed to a higher proportion of OSA among BQ low risk participants than intended. Thus, this bias would have contributed to lower estimated diagnostic properties of the BQ and higher prevalence estimates of OSA if not corrected. Therefore, estimated screening properties of the BQ and estimated prevalences of OSA were calculated by a multivariate logistic regression model that was evaluated by advanced data simulation (appendix 8). This model also accounted for the multi-stage sampling procedure and sub-stratifications in the BQ high risk group.

A limitation to the model was that is was based on the estimation sample (Paper I, table 1) rather than the whole screening sample. However, in the discussion of paper I we argue that this sample was representative of the screening sample because of the lack of differences between these samples.

A final limitation to the statistical model is that the use of the model is founded on the assumption that associations between self-report items used in the statistical model and OSA pathology are constant through the severity specter of the AHI. This assumption can of course be questioned, but we argue in paper I that the internal and external validation procedures of the model secure that the results provided by the model can be generalized to the general population.

Among factors that was not controlled for in the statistical model, the use of exclusion criteria during telephone approach of randomly drawn persons might have influenced the results. Physiological changes in pregnancy were expected to affect both reported daytime sleepiness and biomarkers assessed in other sub-studies of the ASAP. Moreover, limitations of the sleep laboratory prevented persons with physical disabilities to attend. Exclusion by pregnancy and physical disabilities probably affected estimated properties of the BQ and the prevalence estimates to a minor degree. However, exclusion of persons with prior CPAP treatment to the clinical samples probably contributed to an underestimation of screening properties of the BQ and prevalence of OSA because persons with presumably moderate to severe OSA were excluded. Moreover, the PSG equipment was incompatible with the use of CPAP masks, and sleep registration without treatment was considered both unethical and scientifically wrong because sleep registration without such masks would affect the relations to psychiatric disorders and cognitive function measured prior to sleeping. The underestimation potentially caused by excluding persons with CPAP treatment was also counterbalanced by a participant dependent selection mechanism: Analyses of participation bias indicated that persons previously treated for sleep disorders were more likely to participate than untreated persons. The proportion of participants in the ASAP sample with previous treatment of sleep disorders was 10.2%, which was significantly higher than the proportion among non-participants (6.3%). Moreover, 12.2% of participants with OSA (AHI ≥ 5) in the ASAP sample had previously received treatment for sleep disorders, which was significantly higher than 6.9% among participants without OSA. Thus, this bias probably contributed to an overestimation of BQ screening properties and the prevalence of OSA with opposite effect than the effect of the bias caused by excluding CPAP-users.

Exclusion (paper I) of participants with total sleep time <240 minutes or no rapid eye movement sleep was also not adjusted for in the statistical model. This exclusion criteria was adapted from the Wisconsin Sleep Study (Young *et al.* 1993). The decision to exclude these participants was made in order to strengthen reliability of the reference standard polysomnography when calculating prevalence estimates and screening properties of the

Berlin Questionnaire. When compared to the clinical sample in paper I, these 17 persons did not differ significantly regarding AHI or sex. However, the 17 persons were significantly older (55.3 years) than persons included in the clinical sample of paper I (48.3 years, p = 0.012). Accordingly, despite the benefit of improving the reference standard by excluding these persons, the decision might have reduced the effect of older age in the model. On the other hand, the mean age of participants of the clinical sample in paper I was higher than the mean age in the screening sample. Thus, the bias probably has little impact on external validity. In paper II and III, persons with poor sleep quality were not excluded from analyses.

Regarding the clinical sample in paper II and III the consecutive inclusion of 290 BQ high risk participant out of a total of 378 eligible participants in the ASAP sample potentially influenced the internal validity. When comparisons were made between this sample and the remaining 88 BQ high risk participants not included in the sample, no differences in the variables examined were found except for age. The mean age of participants in the clinical sample in paper II and III was 48.2 years while among non-participants it was 51.1 years (p= 0.033). Thus, because age was found to be a strong predictor of cognitive function, this selection might have increased cognitive test scores in paper II. On the other hand, because the participants of the psychosomatic sample did not differ significantly from the 88 BQ high risk non-participants regarding BDI sum score or ESS sum score, and because age was not significantly related to the risk of having psychiatric disorders, the impact of this selection on the results in paper III is probably minor.

Participant-dependent factors

The main participant dependent bias in addition to the selection of persons previously treated for OSA as described above was the selection of persons with daytime somnolence or daytime sleepiness in the BQ high risk group as indicated in Table 3. Persons with BQ high risk experiencing daytime sleepiness were more likely to participate in the study than persons without daytime sleepiness. However, the proportion of persons reporting frequent depressive thoughts was not different between participants and non-participants (Table 3). In order to gain further knowledge of the effect of this participation bias on BQ high risk status, the following post-hoc analysis was performed: Table 5 present possible combinations of BQ high risk in the screening sample and Table 6 presents the same data in the clinical sample from paper I.

Table 5: Percentage distribution between Berlin Questionnaire sub-groups in the screening sample in total and by age ≥ 50 years and male sex

BQ high risk, N= 3960	Age ≥ 50	Males
Snoring and somnolence, N=1336 (33.7%)	26.1 %	33.5 %
Snoring and obesity/HT, N=1462 (36.9%)	45.5 %	41.0 %
Somnolence and obesity/HT, N=306 (7.7%)	7.2 %	4.4 %
All risk categories, N= 856 (21.6%)	21.1 %	21.1%

BQ = Berlin Questionnaire, HT = hypertension,

Table 6: Percentage distribution between Berlin Questionnaire sub-groups in the clinical sample from paper I in total and by age ≥ 50 years and male sex

BQ high risk, N= 365	Age ≥ 50	Males
Snoring and somnolence, N=125 (34.2%)	24.9 %	34.3 %
Snoring and obesity/HT, N=110 (30.1%)	37.6 %	34.3 %
Somnolence and obesity/HT, N=33 (9.0%)	10.2 %	3.9 %
All risk categories, N= 97 (26.6%)	27.4 %	27.5%

BQ = Berlin Questionnaire, HT = hypertension,

Within the tables, stratification by age and sex seem to affect the internal distribution between BQ sub categories to a larger extent than selection from the screening sample to the clinical sample in paper I observed when comparing the tables. Selection bias by subjective sleep complaints thus appears to affect BQ sub categories to a minor extent when compared to selection by age and sex. Subsequently, these post-hoc analyses illustrates that both age and gender influence the internal distribution of BQ high risk which should be considered when interpreting the results of paper II and III. For example, the risk of having a psychiatric disorder was higher and the risk of having OSA was lower in females (paper III, Table 3). Because lesser females than males were found in combinations with snoring and somnolence and snoring and obesity/hypertension, the internal distribution of BQ high risk thus might have inflated confounding by sex in paper III. However, adjustment for sex did not significantly alter the associations observed between psychiatric disorders and OSA.

External validity

Regarding external validity of results from the screening sample, the main limitation to generalizing to the general population is the response rate. Although the response rate of 55.7% in the ASAP was better than response rates of 20% and 22% respectively in the two US studies that previously have used the BQ in a general population setting (Hiestand *et al.*

2006;Kapsimalis and Kryger 2009), response bias might have influenced all results presented in this thesis. In order to assess any impact of response bias, we assessed differences in the response rates (appendix 4) regarding age and gender. The response rate to the screening sample was significantly higher for subjects aged 50 years and more (62.0%) than for persons less than 50 years of age (50.1%), and was higher for females (59.0%) than males (52.4%). Thus, all estimates in this thesis are more precise for persons aged 50 years or more compared to persons less than 50 years of age and for females compared to males in the general population.

In addition to age- and gender, we believe the most likely factor of systematic selection (if any) between responders and non-responders to our questionnaire were subjective sleep complaints. We therefore also compared sleepiness in the screening sample with a representative, Norwegian study assessing sleepiness by the same questionnaire (Pallesen *et al.* 2007). The mean age in this study was 47.6 years, the mean self- reported BMI was 24.7 and the mean ESS score was 7.0, which is almost identical to the ESS score found in the screening sample of our study. The similarity with this other Norwegian, general population sample strengthens the external validity of the screening sample.

Finally, regarding sleepiness, it is worth noting that the prevalence of EDS in the Norwegian general population as defined by an ESS >10 in the study by Pallesen et al. and in the screening sample both was 17.7% (Pallesen *et al.* 2007). When compared to the original general population prevalence estimate of 5.9% with EDS by Johns et al. (Johns 1991), Norwegian adults today report more sleepiness than Australian adults reported 20 years earlier.

Regarding external validity of the estimates in paper I, the use of cut-off values of the AHI as a diagnostic criterion for OSA is not directly comparable to a diagnosis of OSA. According to the ICSD-2 criteria (table 1), all BQ high risk participants with AHI >5 by definition fulfill the B criterion for OSA. However, some BQ low risk participants with an AHI >5 did not fulfill the symptom criterion for OSA. Moreover, the ICSD-2 D criterion states that "the disorder is not better explained by another current sleep disorder, medical or neurological disorder, medication use or substance use disorder". Thus, it is important to bear in mind that OSA diagnosed by a simple cut-off value of the AHI is not directly comparable to a clinical diagnosis of OSA as defined by the ICSD-2.

Regarding paper II and III, the external validity of the BQ high risk clinical sample in paper II and III is only directly comparable to persons with BQ high risk in the general population. However, although not directly comparable to the general population as a whole,

the results in paper II and III add knowledge from a community-based sample to complex associations between OSA and cognitive function and psychiatric disorders respectively.

5.1.3 Assessments

The verification of data quality by two investigators, minimizing random errors in creating the database increases the reliability of the results assessed. Moreover, the prospective collection of clinical data by established methods, performed standardized and punched into the research database by few investigators also increases the reliability in general.

The screening questionnaire

Data from each of the three BQ symptom categories might be affected by information bias. Self-reported snoring is in most cases dependent of a bed partner that actually acknowledge the symptoms to occur while the person is sleeping. Moreover, the BQ has a "don't know" response alternative that affect psychometric properties (Fedson *et al.* 2012). However, there is a lack of consensus over how to analyze such responses.

Regarding the BQ somnolence category, the time frame is diffuse. This may in particular affect the question regarding falling asleep while driving. Inclusion of the additional question used by Hiestand et al. and Kapsimalis and Kryger regarding frequency of falling asleep while driving could thus have altered the properties of the BQ somnolence category (Hiestand *et al.* 2006;Kapsimalis and Kryger 2009). More importantly, the construct of sleepiness is complex (Cluydts *et al.* 2002), and self-report of daytime somnolence or sleepiness has been shown to be influenced more strongly by symptoms of depression than OSA severity in another community-based sample (Bixler *et al.* 2005). Finally, in a study from 1997, Engleman et al. compared pre- and post treatment ESS scores of sleepiness prior to treatment and found that participants with OSA systematically underscored sleepiness prior to treatment (Engleman *et al.* 1997).

The reliability of data in the BQ risk category based on self-reported hypertension and obesity is to a lesser degree affected by information bias. However, health seeking bias will obviously affect the reliability of these data to some extent. Unfortunately, community-based studies of the relationship between self-reported hypertension and measured hypertension could not be identified.

Regarding the ESS, A Norwegian version with a slightly different translation regarding the Norwegian word for "dozing off" has recently been validated (Beiske *et al.* 2009). This Norwegian version of the ESS had acceptable internal consistency and test-retest reliability with internal consistency reliability, as assessed with Cronbach's alpha, of 0.8 and

test–retest reliability of 0.8, as assessed with the intra-class correlation coefficient. In the study by Beiske et al., as in other validation studies of the ESS, individual items and the ESS score was only fair to moderately associated with results from the multiple sleep latency test.

Polysomnography

A major strength of this study was that sleep was assessed by polysomnography. However, it was decided to rely on a clinical scoring rather than a scientific scoring algorithm. As illustrated in Figure 1, the spectrum of sleep disturbed breathing is broader than the spectrum of OSA. Thus, a more comprehensive assessment of sleep containing both respiratory related arousals and assessment of pCO_2 would have given information regarding the whole spectrum of sleep disturbed breathing. It is also worth noting that scoring with other definitions of obstructive events, including different thresholds of desaturation regarding hypopneas, could have influenced the results presented in the thesis (Redline *et al.* 2000). Hypopneas were only scored by a pre-defined definition of $\geq 4\%$ oxygen desaturation. Moreover, neither arousals nor pCO_2 is usually registered in clinical practice. Accordingly, the focus on OSA as assessed by the AHI or oxygen variables in this study thus reflects everyday clinical practice.

Moreover, the use of only one single, sleep registration is a potential limitation to the reliability of sleep assessment (Stepnowsky, Jr. *et al.* 2004). Ideally, sleep should be measured twice, but in accordance with most previous studies that have assessed screening properties of the BQ or prevalence of OSA, we chose to rely on a single measure of sleep. However the use of an in-hospital assessment of sleep strengthened the internal validity of the PSG assessments compared to studies that have relied on portable solutions. Participants thus went to sleep at will without potential disturbing factors in a home setting, and remained sleeping until naturally awake.

The use of two scorers also was a potential limitation to the PSG data although they were completely blinded for BQ risk status. Inter rater reliability between these two raters was not assessed. However, these two raters have co-operated for almost 10 years, they were licensed simultaneously and they arrange courses in PSG-scoring in Norway together every year. It is therefore likely that they score sleep relatively similarly.

Another approach that increased the reliability of the PSG assessments was the screening for artifacts in oximetry data. In particular, variables measured at one or a few time points during the night (lowest oxygen saturation and time below 90% saturation) are vulnerable to artifacts. At the contrary, variables such as the mean oxygen saturation and the oxygen desaturation index are measured over a longer period of time. Accordingly, the effect

of artifacts is attenuated in these variables. However, results in paper II and III were only changed to a minor degree when artifacts in oxygen variables had been removed.

Cognitive tests

Cognitive function was assessed by the same physician at identical time points the day prior to polysomnography, thus eliminating problems with inter-rater reliability. Moreover, the tests were chosen from a list proposed by Decary et al. (Decary *et al.* 2000) for use in OSA patients. However, the limited number of tests increased the probability of a type two statistical error (i.e., finding no association when the association is truly present).

Unfortunately, intra-rater reliability was not assessed regarding the neurocognitive testing. However, I was comprehensively trained by Professor Kjetil Sundet prior to presenting the tests to the participants of the study.

The tests should ideally have been performed after the sleep studies. However, with the chronic nature of OSA, I believe the validity of the neurocognitive assessments was only to a minor degree affected by this limitation.

Finally, it is conceptually problematic to assess higher brain functions related to OSA without also assessing the underlying level of alertness (Verstraeten and Cluydts 2004). In the Stroop test, speed is adjusted for. However, regarding the RAVLT, the influence of alertness on the results is not known.

Psychiatric assessments

The SCID-I interview yields highly reliable diagnoses of DSM–IV axis I disorders and is often considered as the gold standard of diagnostic assessments in clinical research.
In the present study, one physician underwent extensive training in performing the interview. In addition, all interviews were taped. The finding of an excellent inter-rater reliability strengthens the reliability of the diagnoses obtained.

The diagnostic approach by the SCID-I in this thesis was included in the SCID manual. Thus, only the somatoform dimension of pain was assessed. Valuable information regarding other somatoform symptoms such as nausea, dizziness, bowel symptoms etc. was therefore not registered.

Further, because of low prevalence on each anxiety disorder, I chose to merge all anxiety disorders into one category of current anxiety. This choice clearly leads to a loss of information regarding the complexity of anxiety disorders.

Regarding the BDI, the internal consistency was satisfactory, as evaluated by Crohnbach's alpha. However, previous studies of the BDI in various populations have demonstrated excellent psychometric properties of this questionnaire.

Demographic variables

The assessment of demographic variables was mainly based on computerized versions of validated questionnaires. Most participants managed to complete these versions without help. However, when assistance was needed, it is possible that this assistance might have influenced responses to some extent. However, all physicians involved in the collection of data were instructed not to provide other than technical support.

5.1.4 Summary of methodological considerations

Acknowledging the methodological strength and weaknesses discussed above, I regard the samples defined and the data collected reliable and valid for answering the research questions of this study. However, post-hoc analyses of internal validity and analyses of external validity of the screening questionnaire indicated that a particular focus should be given to the effect of age, gender and obesity when interpreting the results of this study.

Regarding generalizability, the results from paper I can be generalized to the general population while level of cognitive function and prevalences of psychiatric disorders reported in paper II and III should be generalized only to a community-based BQ high risk population. On the other hand, given the limitations discussed above, I regard the community-based clinical sample in paper II and III suitable for assessing associations between OSA, cognitive function and psychiatric disorders respectively.

5.2.0 Results and Clinical Implications

5.2.1 BQ screening properties in the general population

The proportion of persons categorized to be at high risk for OSA in the screening sample was consistent with other studies that have distributed the BQ to a general population sample (Hiestand *et al.* 2006;Kapsimalis and Kryger 2009;Shepherd *et al.* 2011). However, the estimated diagnostic properties of the BQ when distributed to a general population sample were found to be sub-optimal. No previous studies of BQ properties when distributed to a general population sample could be identified. Little is also known regarding properties of other screening questionnaires for OSA when distributed to general population samples (Abrishami *et al.* 2010;Harding 2001;Pang and Terris 2006;Rowley *et al.* 2000). However, a

poster presented in the "Sleep 2011" in Minneapolis replicated our findings regarding screening properties of the BQ when being administered to a Swiss general population (Andries 2011). Finally, the study by Gantner et al. also reported sub-optimal properties of the BQ when distributed to a general population sample with high cardiovascular risk (Gantner *et al.* 2010).

A major challenge when interpreting screening properties of the BQ in a general population sample is how to understand sub groups of BQ high risk persons. As presented in Table 5 and 6, age and gender were found to be differently related to each sub group of BQ high risk. Moreover, Table 7 illustrates that also unadjusted screening properties varied between BQ high risk combinations.

Table 7: Unadjusted diagnostic properties of the Berlin Questionnaire and Berlin Questionnaire risk groups.

Total sample: N= 518	**AHI ≥ 5**	**AHI < 5**	**AHI ≥ 15**	**AHI < 15**
BQ high risk, N= 365	**227**	**138**	**130**	**235**
Snoring and somnolence, N=125 (34.2%)	66	59	28	97
Snoring and obesity/HT, N=110 (30.1%)	78	32	51	59
Somnolence and obesity/HT, N=33 (9.0%)	14	19	5	28
All risk categories, N= 97 (26.6%)	69	28	46	51
BQ low risk, N= 153	**61**	**92**	**27**	**126**
Diagnostic properties:				
LR+ (CI)	1.3 (1.2, 1.5)*		1.3 (1.1, 1.4)*	
LR+ by snoring and somnolence	1.3 (1.0, 1.7)		1.2 (0.9, 1.6)	
LR+ by snoring and obesity/HT	2.2 (1.6, 3.0)*		2.1 (1.6, 2.7)*	
LR+ by somnolence and obesity	1.1 (0.6, 2.0)		0.9 (0.4, 2.1)	
LR+ by all risk categories	2.3 (1.6, 3.3)*		2.2 (1.6, 2.9)*	
LR- (CI)	0.5 (0.4, 0.7)*		0.5 (0.3, 0.7)*	
LR- by snoring and somnolence	0.8 (0.6, 1.0)		0.9 (0.6, 1.2)	
LR- by snoring and obesity/HT	0.6 (0.5, 0.7)*		0.5 (0.4, 0.7)*	
LR- by somnolence and obesity/HT	1.0 (0.9, 1.1)		1.0 (0.9, 1.2)	
LR- by all risk categories	0.6 (0.5, 0.8)*		0.5, 0.4, 0.7)*	

AHI= Apnea Hypopnea Index, BQ = Berlin Questionnaire, HT = hypertension, CI = Confidence Interval, LR+ = Likelihood Ratio for AHI above cut-off, LR- = Likelihood Ratio for AHI below cut-off , * = LR significantly different from 1

The table illustrates that unadjusted screening properties of the BQ as indicated by likelihood ratios varied to an extensive degree between BQ sub-groups. Only ratios are presented in order to avoid weighting for different size of the BQ high risk sub-groups. The unadjusted positive and negative likelihood ratios for the BQ high risk versus BQ low risk indicate that screening properties were better in BQ risk groups without the BQ somnolence category than in BQ risk groups with the BQ somnolence category. I thus believe the relation between BQ somnolence or sleepiness and OSA is a key factor in interpreting the results of paper II and III.

The effect of different BQ screening properties regarding age and sex is best illustrated in Table 3 in paper III where the odds of having OSA defined as AHI ≥ 5 is reported to be significantly higher in males compared to females and in persons ≥ 50 years of age compared to persons less than 50 years. At the same time, the odds of having psychiatric disorders showed the opposite pattern. Accordingly, the BQ performed worse in sub-groups with high risk of psychiatric disorders. In line with the findings by Bixler et al. (Bixler *et al.* 2005), sleepiness was also higher in these sub-groups of the BQ.

In addition to the strong association between sleepiness and psychiatric disorders in the general population, a potential mechanism for the inverse relation between sleepiness and OSA reported in this thesis is the underreporting of sleepiness in OSA as discussed above (Engleman *et al.* 1997) and the differences between objective and subjective sleepiness per se (Cluydts *et al.* 2002).

The estimated BQ properties were also highly dependent on the definition of OSA applied. If we had chosen to define OSA by the AHI and daytime somnolence, screening properties would have increased. However, in that case, the reference standard would be partially the same as the instrument validated which is methodologically dubious. Moreover, there is an on-going discussion regarding the utility of daytime symptoms as a diagnostic criterion for OSA. The ICSD-2 definition for OSA opens for a diagnosis of OSA regardless of daytime symptoms in persons with an AHI > 15 (Table 1). At the contrary, it has been reported that for example hypertension is only related to OSA in persons that experience sleepiness (Kapur *et al.* 2008). Moreover, the first longitudinal study of predictive abilities of the BQ reports that BQ high risk predicts death censored graft loss in kidney transplant recipients (Szentkiralyi *et al.* 2011). Thus, although BQ high risk is sub-optimal for identifying OSA in the general population, only longitudinal studies can address the predicting properties of BQ high risk status in the general population.

5.2.2 Prevalence of OSA

The prevalence of OSA had not previously been estimated in a Norwegian general population. The age- and sex specific estimates generated by our statistical model were approximately equal to and slightly higher than previous estimates from the Wisconsin Sleep Cohort and Pennsylvania State Cohort (Bixler *et al.* 1998;Bixler *et al.* 2001;Young *et al.* 1993), but much higher than previous Scandinavian estimates (Gislason *et al.* 1988;Jennum and Sjol 1992). Our estimates were slightly lower than previous estimates from Spain, Poland and Australia (Bearpark *et al.* 1995;Duran *et al.* 2001;Plywaczewski *et al.* 2008) and much lower than a recent prevalence estimate from Brazil (Tufik *et al.* 2010). Unfortunately, in many of the previous studies the BMI has not been reported. However, according to official statistics from the USA and Norway the proportion of adults with obesity has increased by more than 10% since the first of these studies was published in 1988 (www.nih.gov, www.fhi.no). It is therefore not surprising that the estimated prevalence of OSA in the current study is higher than that obtained in older US and Scandinavian estimates.

In addition to the effect on estimated properties of the BQ as discussed above, the choice to define OSA based on a cut-off on the AHI also affected the prevalence estimates reported. It would have been possible to calculate prevalences of OSA defined also by sleepiness or daytime somnolence. However, I chose not to do so because of multiple factors affecting self-reported sleepiness in the general population as revealed in this discussion.

Finally, as previously emphasized by Lindberg and Gislason and by Redline et al. (Lindberg and Gislason 2000;Redline *et al.* 2000), analyses by alternative respiratory variables than the AHI would have altered the prevalence estimates. For example, if only the apnea index had been used for analysis, the prevalence estimates would have been lower. Moreover, as indicated in Figure 1, specific focus on central apneas during analyses, eventually combined with assessment of venous base deficit or PCO_2 could have identified obesity hypoventilation syndrome as a specific diagnostic entity within the study population. The most recent report of health, social and economical consequences of sleep-disordered breathing reported almost threefold costs in patients with obesity hypoventilation syndrome when compared to patients with OSA (Jennum and Kjellberg 2011). At the other end of the severity scale in Figure 1, scoring of respiratory related arousals would have yielded higher prevalence estimates of OSA.

5.2.3 OSA severity, verbal memory and executive function

To my knowledge, no prior study had described verbal memory and executive function in community-dwelling adults at high risk of having OSA, as identified by the BQ. Regarding associations studied between measures of cognitive function and OSA severity, verbal memory was found to be independently related to average oxygen saturation. Executive function was not related to any of the pre-defined variables assessing OSA severity. The AHI, which is the most commonly used measure when assessing OSA severity, was only related to cognitive function in bivariate analyses. The arousal index was not related to cognitive function in any analysis.

The recruitment of participants by the BQ in this study resulted in a clinical sample with a relatively low median AHI of 7.7 (25^{th} percentile = 2.4, 75^{th} percentile = 22.2) compared with clinical studies of OSA. However, more than one-third of the sample had an AHI of ≥ 15, which is the criterion for moderate to severe OSA (American Academy of Sleep Medicine 2005). However, as discussed in section 5.2.1, the age- and gender distribution within the BQ high risk group might have contributed to a bias towards the null hypothesis because persons without OSA were younger and more likely to be female than persons with OSA.

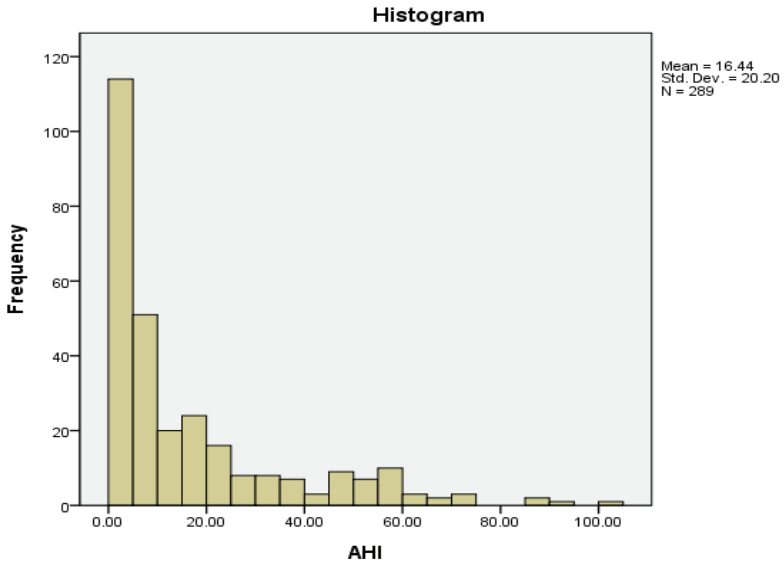
We chose to present raw scores from the RAVLT and the Stroop test followed by adjustments in a linear regression model. An alternative approach more easily interpreted by clinicians would have been to present norm-based results. However, because cognitive function was not assessed in BQ low risk participants, it was chosen to focus on the relation between cognitive function and OSA rather than norm-based results.

Studies in the last five years have confirmed that verbal memory in particular is affected by OSA pathology (Naegele *et al.* 2006;Twigg *et al.* 2010). On the other hand, the association between OSA and the complex executive function may be spurious (Quan *et al.* 2006;Saunamaki *et al.* 2009;Twigg *et al.* 2010) and potentially influenced by attention (Gosselin *et al.* 2006;Verstraeten and Cluydts 2004).

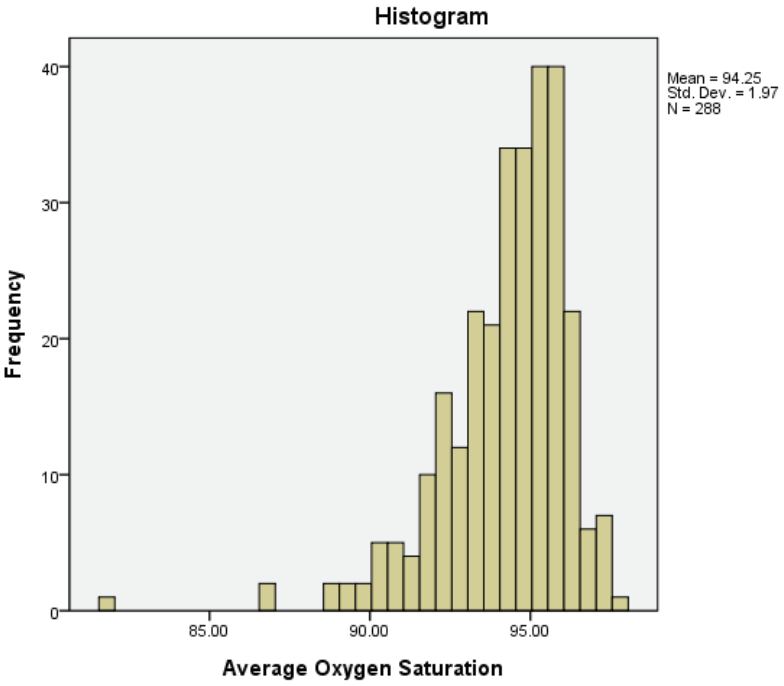
Because verbal memory was associated to OSA severity assessed by average oxygen saturation but not as assessed by the AHI, it is important to emphasize that average oxygen saturation and the AHI had slightly different statistical distributions (figure 5 a and b).

Figure 5a: Distribution of the apnea hypopnea index (a) and average oxygen saturation (b) in the psychosomatic sub-sample

a



b



I do not know why the distribution of average oxygen saturation was more bell-shaped than the distribution of the AHI. However, this observation indicates that the two measures of OSA severity assess slightly different aspects of OSA. In paper II, the possible effect of other respiratory disorders than OSA on the oxygen curve is discussed. The conclusion of the discussion was that such effects were not likely because the prevalence of other respiratory disorders in the sample was low. Our finding of an independent association between average oxygen saturation and verbal memory is also in line with a recent study of cerebrovascular regulation in community-dwelling adults (Morgan *et al.* 2010). Thus, although this measure of OSA severity does not capture the episodic nature of breathing in OSA, is a promising supplement to the AHI in the understanding of OSA pathology.

In paper II, the relation between average oxygen saturation and verbal memory was adjusted for potential confounding by age, gender, higher education and body mass index. The model explained 20% of the variance in cognitive function. When MDD or any psychiatric disorder was added to the model (data not reported), 21% of the variance was explained. Moreover, when psychiatric disorders were entered into the regression models as independent variables, they significantly contributed. This finding is in line with the study by Cross et al. that reported exacerbated neural injury in OSA patients with depression compared to OSA patients without depression (Cross *et al.* 2008). This indication of an interactive effect of depression and OSA on cerebral function may be mediated by metabolic factors or systemic inflammation. In another paper from the study sample in paper II and III, we have shown an association between high sensitivity C-reactive protein and psychiatric morbidity (Einvik *et al.* 2011). However, it is beyond the scope of this thesis to address this particular discussion. Moreover, psychiatric disorders were not entered into the final models of paper II because of difficulties in determining the direction of causality between OSA, cognitive function and psychiatric disorders. In other words, impaired cognitive function can theoretically be both caused by psychiatric disorders and cause psychiatric disorders. Accordingly, the association between cognitive function and psychiatric disorders was not assessed in this thesis.

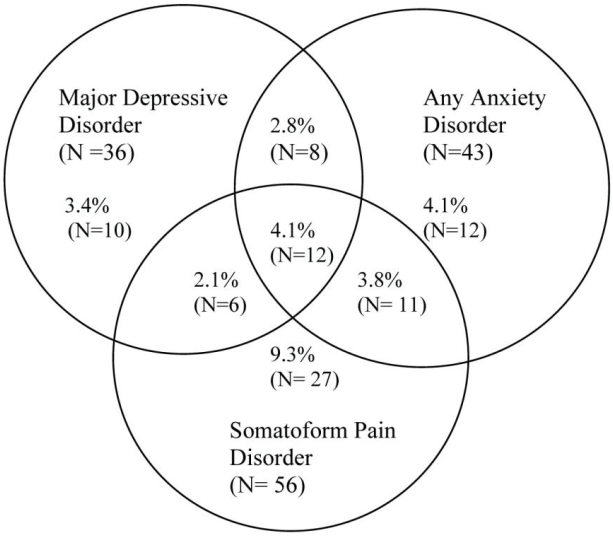
5.2.4 OSA, depression and somatoform pain

Our finding of a high prevalence of psychiatric disorders in a BQ high-risk sample representative of the general population is in line with two previous studies (Hiestand *et al.* 2006;Kapsimalis and Kryger 2009). The study by Hiestand et al. reported a prevalence of depression in 33.0% and anxiety in 18% of BQ high risk respondents of the 2005 “Sleep in

America poll". The study by Kapsimalis et al. reported a prevalence of depression in 41.0% and anxiety in 22% of BQ high risk female respondents of the 2007 poll (Kapsimalis and Kryger 2009). These proportions were based on self-report of psychiatric diagnoses, which can explain the somewhat higher estimates than those reported in our study.

In addition to a high prevalence of psychiatric disorders, Figure 6 demonstrates a high degree of co-morbidity between different psychiatric disorders in the psychosomatic sample.

Figure 6: Co-morbidity between psychiatric disorders



The co-morbidity illustrated in the figure is in line with previous studies of psychiatric disorders in the general population at the time of planning this thesis (Wittchen and Jacobi 2005). A recent update of this review also included sleep disorders to the size and burden of mental disorders in Europe (Wittchen *et al.* 2011). In this review, the prevalence of mental disorders changed to a minor extent. However, nonorganic insomnia was found to be present in 7% and OSA in 3% of the general European population. Thus, in addition to the co-morbidity displayed in Figure 6, there is probably also an overlap between OSA and insomnia that has not been emphasized in this thesis (Bjornsdottir *et al.* 2012).

Regarding the association between OSA and psychiatric disorders, the findings that neither of MDD, current anxiety and somatoform pain disorder were associated with OSA has important implications for the interpretation of previous studies that have reported positive

associations between OSA and symptoms of psychiatric disorders (Aikens and Mendelson 1999;Bardwell *et al.* 1999;Kales *et al.* 1985;Sharafkhaneh *et al.* 2005). Most community-based studies of this relationship have concluded that OSA seems to be an independent risk factor for symptoms of depression as assessed by questionnaires (Ohayon 2003;Peppard *et al.* 2006;Sivertsen *et al.* 2008). In contrast, our data support community-based studies that have partly or completely failed to establish an independent association between OSA and depression (Enright *et al.* 1996;Kripke *et al.* 1997). However, only two previous, community-based studies concerning the relation between OSA and depression have assessed sleep with objective measures (Kripke *et al.* 1997;Peppard *et al.* 2006). In a sample with median 4% oxygen desaturation index of 4.3 in females and 6.7 in males, Kripke et al. found no association between symptoms of depression and OSA (Kripke *et al.* 1997). In contrast, Peppard et al. using a sample in which 6% of the females and 14% of the males showed an AHI $\geq$ 15, found a positive dose-response association between SRBD and depression (Peppard *et al.* 2006). The severity of OSA in our BQ high risk sample was higher than in these samples. Moreover, as presented in an on-line supplement to paper III (appendix 9), alternative definitions of OSA did only result in minor changes to our findings.

The association between OSA and symptoms of depression was also assessed in an auxiliary sample consisting of all BQ low risk participant in the ASAP. These analyses revealed that both the mean BDI sum and the median AHI were 50% lower than in the BQ high risk sample. Moreover, also in this BQ low risk sample, BDI scores did not differ significantly between those with OSA and those without OSA. Consequently these findings from the auxiliary sample imply that the high level of psychiatric co-morbidity observed among BQ high risk participants more likely is related to properties of the BQ rather than being an effect of OSA as such. This interpretation is in line with Andrews et al. who hypothesized that shared co-factors between depression and OSA rather than apneas and hypopneas per se explain the association between OSA and symptoms of depression found in multiple studies of clinical samples (Andrews and Oei 2004). Moreover, in the study by Peppard et al. (Peppard *et al.* 2006), also important effects of putative confounders on the said association were reported. We therefore believe that our findings contribute to an elucidation of the complex association between OSA, psychiatric disorders and cardinal symptoms of OSA.

Finally, in line with a recent review of epidemiology of OSA, the estimation of a high prevalences of OSA with subsequent sub-optimal screening properties of the BQ in a general population sample emphasizes the need for improved screening models for OSA and

sleep-disordered breathing (Jennum and Riha 2009). Moreover, the finding of an association between average oxygen saturation and verbal memory and the finding of a negative association between any psychiatric disorder and OSA among persons with BQ high risk in the general population are reminders of the complexity of these associations. This complexity ranges from "various circumstances" causing selection bias to studies of clinical populations to the distribution of screening factors for OSA in community-based studies of OSA. Accordingly, clinicians treating OSA need to carefully evaluate the effect of these "various circumstances," such as age, sex, obesity, psychiatric disorders, cognitive functioning and effects of everyday distress when confronted with the patient with OSA.

6.0.0 Conclusion and clinical implications

This thesis has focused on screening properties of the BQ, prevalence of OSA, cognitive function and psychiatric disorders. The following conclusions are drawn:

- One out of four respondents of the BQ was classified at high risk of having OSA. However, the screening properties of the BQ were sub-optimal.
- The prevalences of OSA defined by AHI ≥ 5 and by AHI ≥ 15 in a Norwegian general population sample were estimated to be 16% and 8% respectively.
- Cognitive test scores from participants with high risk for OSA were comparable to scores of persons 20-30 years older than the age of the participants.
- An independent association between verbal memory and OSA severity as assessed by average oxygen saturation was found.
- MDD, current anxiety disorder and somatoform pain disorder were diagnosed in 12.4%, 14.8% and 19.3% of community-dwelling adults at a high risk for OSA.
- A negative association between OSA and psychiatric morbidity was found.

7.0.0 Suggestions for future research

- No previous study has validated screening properties of the BQ in a general population sample. Therefore, our findings should ideally be replicated in future community-based studies. However, we believe that future studies assessing properties of the BQ in the general population should modify the scoring algorithm, alternatively assess predictive power of single items or combinations of items. Moreover, the items assessing daytime somnolence should be more precisely formulated or simply replaced by the ESS. Finally, as a result of the findings presented in paper III, assessment of daytime somnolence in the BQ should optimally be weighted according to level of psychiatric co-morbidity.
- This thesis has presented the first, Norwegian prevalence estimate of OSA. Thus, our baseline assessment is suitable for studying the incidence of OSA in the future.
- The novel finding of average oxygen saturation being the most important assessment of OSA severity on cognitive function should be replicated in future studies. Moreover, associations between average oxygen saturation, symptoms and other features of OSA than cognitive function should be further clarified.
- Future research should explore potential biomarkers related to variables assessing OSA severity, cognitive function and psychiatric disorders. In particular, interactive effects of psychiatric morbidity and OSA should be explored in relation to metabolic disturbancies or systemic inflammation.
- More focus should be given to other forms of psychiatric co-morbidity in OSA than depression. In particular somatoform pain, anxiety and insomnia should be explored.
- Information regarding shift work was not registered in this study and collected data regarding perception of sleep complaints, insomnia and sleep related quality of life have not yet been analyzed. These aspects might have given additional information in interpreting sleep variables and should be included in future studies of cognitive function, psychiatric disorders or subjective daytime complaints related to OSA.
- Finally, the baseline examinations of the ASAP consist of an extensive baseline assessment of 535 participants. A goal for future research on the properties of the BQ will be to follow these 535 participants through life.

8.0.0 References

Abrishami, A., Khajehdehi, A. and Chung, F. A systematic review of screening questionnaires for obstructive sleep apnea. *Can. J. Anaesth.*, 2010, 57: 423-438.

Adams, N., Strauss, M., Schluchter, M. and Redline, S. Relation of measures of sleep-disordered breathing to neuropsychological functioning. *Am. J. Respir. Crit Care Med.*, 2001, 163: 1626-1631.

Ahmadi, N., Chung, S. A., Gibbs, A. and Shapiro, C. M. The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance. *Sleep Breath.*, 2008, 12: 39-45.

Aikens, J. E. and Mendelson, W. B. A matched comparison of MMPI responses in patients with primary snoring or obstructive sleep apnea. *Sleep*, 1999, 22: 355-359.

Aloia, M. S., Arnedt, J. T., Davis, J. D., Riggs, R. L. and Byrd, D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. *J. Int. Neuropsychol. Soc.*, 2004, 10: 772-785.

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

American Academy of Sleep Medicine *International classification of sleep disorders: Diagnostic and Coding Manual.* American Academy of Sleep Medicine, Westchester, IL, 2005 (second edition).

Andrews, J. G. and Oei, T. P. The roles of depression and anxiety in the understanding and treatment of Obstructive Sleep Apnea Syndrome. *Clin. Psychol. Rev.*, 2004, 24: 1031-1049.

Andries, D. Berlin Questionnaire Performance for Detecting Sleep Apnea in the General Population . Poster 0366 presented at Sleep 2011, Minneapolis . 2011.

Banno, K. and Kryger, M. H. Sleep apnea: clinical investigations in humans. *Sleep Med.*, 2007, 8: 400-426.

Bardwell, W. A., Berry, C. C., Ancoli-Israel, S. and Dimsdale, J. E. Psychological correlates of sleep apnea. *J. Psychosom. Res.*, 1999, 47: 583-596.

Bearpark, H., Elliott, L., Grunstein, R., Cullen, S., Schneider, H., Althaus, W. and Sullivan, C. Snoring and sleep apnea. A population study in Australian men. *Am. J. Respir. Crit Care Med.*, 1995, 151: 1459-1465.

Beck, A. T., WARD, C. H., MENDELSON, M., MOCK, J. and ERBAUGH, J. An inventory for measuring depression. *Arch. Gen. Psychiatry*, 1961, 4: 561-571.

Beebe, D. W., Groesz, L., Wells, C., Nichols, A. and McGee, K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. *Sleep*, 2003, 26: 298-307.

Beiske, K. K., Kjelsberg, F. N., Ruud, E. A. and Stavem, K. Reliability and validity of a Norwegian version of the Epworth sleepiness scale. *Sleep Breath.*, 2009, 13: 65-72.

Berkson, J. Limitations of the application of fourfold table analysis to hospital data. *Biometrics bulletin*, 1946, 2: 47-53.

Berry, D. T., Phillips, B. A., Cook, Y. R., Schmitt, F. A., Gilmore, R. L., Patel, R., Keener, T. M. and Tyre, E. Sleep-disordered breathing in healthy aged persons: possible daytime sequelae. *J. Gerontol.*, 1987, 42: 620-626.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Calhoun, S. L., Vela-Bueno, A. and Kales, A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J. Clin. Endocrinol. Metab*, 2005, 90: 4510-4515.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Ten, H. T., Rein, J., Vela-Bueno, A. and Kales, A. Prevalence of sleep-disordered breathing in women: effects of gender. *Am. J. Respir. Crit Care Med.*, 2001, 163: 608-613.

Bixler, E. O., Vgontzas, A. N., Ten, H. T., Tyson, K. and Kales, A. Effects of age on sleep apnea in men: I. Prevalence and severity. *Am. J. Respir. Crit Care Med.*, 1998, 157: 144-148.

Bjornsdottir, E., Janson, C., Gislason, T., Sigurdsson, J. F., Pack, A. I., Gehrman, P. and Benediktsdottir, B. Insomnia in untreated sleep apnea patients compared to controls. *J. Sleep Res.*, 2012, 21: 131-138.

Boland, L. L., Shahar, E., Iber, C., Knopman, D. S., Kuo, T. F. and Nieto, F. J. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the Sleep Heart Health Study. *J. Sleep Res.*, 2002, 11: 265-272.

Bridgman, S. A., Dunn, K. M. and Ducharme, F. Surgery for obstructive sleep apnoea. *Bridgman. SA. , Dunn. KM. , Ducharme. F. Surgery for. obstructive. sleep apnoea. The. Cochrane.*

Database. of Systematic. Reviews. : Reviews. 1998. Issue. 1 John. Wiley. & Sons. , Ltd. Chichester, UK DOI. : 10. 1002. /14651858. CD001004., 1998.

Chung, F., Yegneswaran, B., Liao, P., Chung, S. A., Vairavanathan, S., Islam, S., Khajehdehi, A. and Shapiro, C. M. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology*, 2008, 108: 822-830.

Cluydts, R., De, V. E., Verstraeten, E. and Theys, P. Daytime sleepiness and its evaluation. *Sleep Med. Rev.*, 2002, 6: 83-96.

Cross, R. L., Kumar, R., Macey, P. M., Doering, L. V., Alger, J. R., Yan-Go, F. L. and Harper, R. M. Neural alterations and depressive symptoms in obstructive sleep apnea patients. *Sleep*, 2008, 31: 1103-1109.

Decary, A., Rouleau, I. and Montplaisir, J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. *Sleep*, 2000, 23: 369-381.

Dickens, C. *The Pickwick Papers*. Oxford University press, Great Clarendon Street, Oxford OX2 6DP, 1836.

Duran, J., Esnaola, S., Rubio, R. and Iztueta, A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am. J. Respir. Crit Care Med.*, 2001, 163: 685-689.

Egeland, J., Rund, B. R., Sundet, K., Landro, N. I., Asbjornsen, A., Lund, A., Roness, A., Stordal, K. I. and Hugdahl, K. Attention profile in schizophrenia compared with depression: differential effects of processing speed, selective attention and vigilance. *Acta Psychiatr. Scand.*, 2003, 108: 276-284.

Einvik, G., Hrubos-Strom, H., Randby, A., Nordhus, I. H., Somers, V. K., Omland, T. and Dammen, T. Major depressive disorder, anxiety disorders, and cardiac biomarkers in subjects at high risk of obstructive sleep apnea. *Psychosom. Med.*, 2011, 73: 378-384.

Engleman, H. and Joffe, D. Neuropsychological function in obstructive sleep apnoea. *Sleep Med. Rev.*, 1999, 3: 59-78.

Engleman, H. M., Hirst, W. S. and Douglas, N. J. Under reporting of sleepiness and driving impairment in patients with sleep apnoea/hypopnoea syndrome. *J. Sleep Res.*, 1997, 6: 272-275.

Enright, P. L., Newman, A. B., Wahl, P. W., Manolio, T. A., Haponik, E. F. and Boyle, P. J. Prevalence and correlates of snoring and observed apneas in 5,201 older adults. *Sleep*, 1996, 19: 531-538.

Fedson, A. C., Pack, A. I. and Gislason, T. Frequently used sleep questionnaires in epidemiological and genetic research for obstructive sleep apnea: A review. *Sleep Med. Rev.*, 2012.

First Michael B, Spitzer Robert L, Gibbon Miriam and Williams Janet B.W. Structured Clinical Interview for DSM-IV Axis I Disorders, patient edition (SCID-I/P), version 2.0, Norwegian version. 1995. Biometrics Research Department, New York State Psychiatric Institute, 722 West 168th Street New York, New York 10032.

Gami, A. S., Pressman, G., Caples, S. M., Kanagala, R., Gard, J. J., Davison, D. E., Malouf, J. F., Ammash, N. M., Friedman, P. A. and Somers, V. K. Association of atrial fibrillation and obstructive sleep apnea. *Circulation*, 2004, 110: 364-367.

Gantner, D., Ge, J. Y., Li, L. H., Antic, N., Windler, S., Wong, K., Heeley, E., Huang, S. G., Cui, P., Anderson, C., Wang, J. G. and McEvoy, D. Diagnostic accuracy of a questionnaire and simple home monitoring device in detecting obstructive sleep apnoea in a Chinese population at high cardiovascular risk. *Respirology.*, 2010, 15: 952-960.

Gassino, G., Cicolin, A., Erovigni, F., Carossa, S. and Preti, G. Obstructive sleep apnea, depression, and oral status in elderly occupants of residential homes. *Int. J. Prosthodont.*, 2005, 18: 316-322.

Giles, T. L., Lasserson, T. J., Smith, B. J., White, J., Wright, J. and Cates, C. J. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Giles. TL, Lasserson. TJ, Smith. BJ. , White. J. , Wright. J. , Cates. CJ. Continuous. positive. airways. pressure. for obstructive. sleep apnoea. in adults. Cochrane. Database. of Systematic. Reviews. : Reviews. 2006. Issue. 3 John. Wiley. & Sons. , Ltd. Chichester, UK DOI. : 10. 1*, 2006.

Gislason, T., Almqvist, M., Eriksson, G., Taube, A. and Boman, G. Prevalence of sleep apnea syndrome among Swedish men--an epidemiological study. *J. Clin. Epidemiol.*, 1988, 41: 571-576.

Gosselin, N., Mathieu, A., Mazza, S., Petit, D., Malo, J. and Montplaisir, J. Attentional deficits in patients with obstructive sleep apnea syndrome: An event-related potential study. *Clin. Neurophysiol.*, 2006, 117: -2235.

Guilleminault, C., Tilkian, A. and Dement, W. C. The sleep apnea syndromes. *Annu. Rev. Med.*, 1976, 27: 465-484.

Gus, M., Goncalves, S. C., Martinez, D., de Abreu Silva, E. O., Moreira, L. B., Fuchs, S. C. and Fuchs, F. D. Risk for Obstructive Sleep Apnea by Berlin Questionnaire, but not daytime sleepiness, is associated with resistant hypertension: a case-control study. *Am. J. Hypertens.*, 2008, 21: 832-835.

Hallan, H., Romundstad, S., Kvenild, K. and Holmen, J. Microalbuminuria in diabetic and hypertensive patients and the general population--consequences of various diagnostic criteria--the Nord-Trondelag Health Study (HUNT). *Scand. J. Urol. Nephrol.*, 2003, 37: 151-158.

Harding, S. M. Prediction formulae for sleep-disordered breathing. *Curr. Opin. Pulm. Med.*, 2001, 7: 381-385.

Harris, M., Glozier, N., Ratnavadivel, R. and Grunstein, R. R. Obstructive sleep apnea and depression. *Sleep Med. Rev.*, 2009, 13: 437-444.

Hayward, L., Mant, A., Eyland, A., Hewitt, H., Purcell, C., Turner, J., Goode, E., Le, C. A., Pond, D. and Saunders, N. Sleep disordered breathing and cognitive function in a retirement village population. *Age Ageing*, 1992, 21: 121-128.

Hiestand, D. M., Britz, P., Goldman, M. and Phillips, B. Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. *Chest*, 2006, 130: 780-786.

Jennum, P. and Kjellberg, J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. *Thorax*, 2011, 66: 560-566.

Jennum, P. and Riha, R. L. Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *Eur. Respir. J.*, 2009, 33: 907-914.

Jennum, P. and Sjol, A. Epidemiology of snoring and obstructive sleep apnoea in a Danish population, age 30-60. *J. Sleep Res.*, 1992, 1: 240-244.

Jennum, P. and Sjol, A. Snoring, sleep apnoea and cardiovascular risk factors: the MONICA II Study. *Int. J. Epidemiol.*, 1993, 22: 439-444.

Jennum, P. and Sjol, A. Self-assessed cognitive function in snorers and sleep apneics. An epidemiological study of 1,504 females and males aged 30-60 years: the Dan-MONICA II Study. *Eur. Neurol.*, 1994, 34: 204-208.

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

Kales, A., Caldwell, A. B., Cadieux, R. J., Vela-Bueno, A., Ruch, L. G. and Mayes, S. D. Severe obstructive sleep apnea--II: Associated psychopathology and psychosocial consequences. *J. Chronic. Dis.*, 1985, 38: 427-434.

Kapsimalis, F. and Kryger, M. Sleep breathing disorders in the U.S. female population. *J. Womens Health*, 2009, 18: 1211-1219.

Kapur, V., Strohl, K. P., Redline, S., Iber, C., O'Connor, G. and Nieto, J. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep Breath.*, 2002, 6: 49-54.

Kapur, V. K., Resnick, H. E., Gottlieb, D. J. and Sleep Heart Health Study Group Sleep disordered breathing and hypertension: does self-reported sleepiness modify the association? *Sleep*, 2008, 31: 1127-1132.

Kim, H. C., Young, T., Matthews, C. G., Weber, S. M., Woodward, A. R. and Palta, M. Sleep-disordered breathing and neuropsychological deficits. A population-based study. *Am. J. Respir. Crit Care Med.*, 1997, 156: 1813-1819.

Knottnerus J.A *The Evidence Base of Clinical Diagnosis*. BMJ Books, 2002.

Krieger, J., McNicholas, W. T., Levy, P., De, B. W., Douglas, N., Marrone, O., Montserrat, J., Peter, J. H. and Rodenstein, D. Public health and medicolegal implications of sleep apnoea. *Eur. Respir. J.*, 2002, 20: 1594-1609.

Kringlen, E., Torgersen, S. and Cramer, V. A Norwegian psychiatric epidemiological study. *Am. J. Psychiatry*, 2001, 158: 1091-1098.

Kripke, D. F., Ancoli-Israel, S., Klauber, M. R., Wingard, D. L., Mason, W. J. and Mullaney, D. J. Prevalence of sleep-disordered breathing in ages 40-64 years: a population-based survey. *Sleep*, 1997, 20: 65-76.

Landis, J. R. and Koch, G. G. The measurement of observer agreement for categorical data. *Biometrics*, 1977, 33: 159-174.

Lim, J., Lasserson, T. J., Fleetham, J. and Wright, J. Oral appliances for obstructive sleep apnoea. *Lim. J. , Lasserson. TJ, Fleetham. J. , Wright. J. Oral appliances. for. obstructive. sleep apnoea. The. Cochrane. Database. of Systematic. Reviews. : Reviews. 2004. Issue. 4 John. Wiley. & Sons. , Ltd. Chichester, UK DOI. : 10. 1002. /14651858. CD004435. pub2.*, 2004.

Lindberg, E., Berne, C., Elmasry, A., Hedner, J. and Janson, C. CPAP treatment of a population-based sample-what are the benefits and the treatment compliance? *Sleep Medicine. Vol. 7(7)()(pp 553-560), 2006.*, 2006, 553-560.

Lindberg, E., Elmasry, A., Gislason, T., Janson, C., Bengtsson, H., Hetta, J., Nettelbladt, M. and Boman, G. Evolution of sleep apnea syndrome in sleepy snorers: a population-based prospective study. *Am. J. Respir. Crit Care Med.*, 1999, 159: 2024-2027.

Lindberg, E. and Gislason, T. Epidemiology of sleep-related obstructive breathing. *Sleep Med. Rev.*, 2000, 4: 411-433.

Mitrushina, M., Boone, K. B., Razani, J. and D'elia, L. F. *Handbook for naormative data for neuropsychological assessment*. Oxford Press, New York, 2005.

Moreno, C. R., Carvalho, F. A., Lorenzi, C., Matuzaki, L. S., Prezotti, S., Bighetti, P., Louzada, F. M. and Lorenzi-Filho, G. High risk for obstructive sleep apnea in truck drivers estimated by the Berlin questionnaire: prevalence and associated factors. *Chronobiol. Int.*, 2004, 21: 871-879.

Morgan, B. J., Reichmuth, K. J., Peppard, P. E., Finn, L., Barczi, S. R., Young, T. and Nieto, F. J. Effects of Sleep Disordered Breathing on Cerebrovascular Regulation: A Population-Based Study. *Am. J. Respir. Crit Care Med.*, 2010, [Epub ahead of print].

Mustafa, M., Erokwu, N., Ebose, I. and Strohl, K. Sleep problems and the risk for sleep disorders in an outpatient veteran population. *Sleep Breath.*, 2005, 9: 57-63.

Naegele, B., Launois, S. H., Mazza, S., Feuerstein, C., Pepin, J. L. and Levy, P. Which memory processes are affected in patients with obstructive sleep apnea? An evaluation of 3 types of memory. *Sleep*, 2006, 29: 533-544.

Naess, O., Sogaard, A. J., Arnesen, E., Beckstrom, A. C., Bjertness, E., Engeland, A., Hjort, P. F., Holmen, J., Magnus, P., Njolstad, I., Tell, G. S., Vatten, L., Vollset, S. E. and Aamodt, G. Cohort profile: cohort of Norway (CONOR). *Int. J. Epidemiol.*, 2008, 37: 481-485.

Netzer, N. C., Stoohs, R. A., Netzer, C. M., Clark, K. and Strohl, K. P. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann. Intern. Med.*, 1999, 131: 485-491.

Ohayon, M. M. The effects of breathing-related sleep disorders on mood disturbances in the general population. *J. Clin. Psychiatry*, 2003, 64: 1195-1200.

Ohayon, M. M., Guilleminault, C., Priest, R. G. and Caulet, M. Snoring and breathing pauses during sleep: telephone interview survey of a United Kingdom population sample. *BMJ*, 1997, 314: 860-863.

Pallesen, S., Nordhus, I. H., Omvik, S., Sivertsen, B., Tell, G. S. and Bjorvatn, B. Prevalence and risk factors of subjective sleepiness in the general adult population. *Sleep*, 2007, 30: 619-624.

Pang, K. P. and Terris, D. J. Screening for obstructive sleep apnea: an evidence-based analysis. *Am. J. Otolaryngol.*, 2006, 27: 112-118.

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

Peppard, P. E., Szklo-Coxe, M., Hla, K. M. and Young, T. Longitudinal association of sleep-related breathing disorder and depression. *Arch. Intern. Med.*, 2006, 166: 1709-1715.

Plywaczewski, R., Bednarek, M., Jonczak, L. and Zielinski, J. Sleep-disordered breathing in a middle-aged and older Polish urban population. *J. Sleep Res.*, 2008, 17: 73-81.

Principe-Rodriguez, K., Strohl, K. P., Hadziefendic, S. and Pina, I. L. Sleep symptoms and clinical markers of illness in patients with heart failure. *Sleep Breath.*, 2005, 9: 127-133.

Punjabi, N. M., Caffo, B. S., Goodwin, J. L., Gottlieb, D. J., Newman, A. B., O'Connor, G. T., Rapoport, D. M., Redline, S., Resnick, H. E., Robbins, J. A., Shahar, E., Unruh, M. L. and Samet, J. M. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS. Med.*, 2009, 6: e1000132.

Quan, S. F., Wright, R., Baldwin, C. M., Kaemingk, K. L., Goodwin, J. L., Kuo, T. F., Kaszniak, A., Boland, L. L., Caccappolo, E. and Bootzin, R. R. Obstructive sleep apnea-hypopnea and neurocognitive functioning in the Sleep Heart Health Study. *Sleep Medicine*, 2006, 7: 498-507.

Redline, S., Kapur, V. K., Sanders, M. H., Quan, S. F., Gottlieb, D. J., Rapoport, D. M., Bonekat, W. H., Smith, P. L., Kiley, J. P. and Iber, C. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *Am. J. Respir. Crit Care Med.*, 2000, 161: 369-374.

Redline, S., Strauss, M. E., Adams, N., Winters, M., Roebuck, T., Spry, K., Rosenberg, C. and Adams, K. Neuropsychological function in mild sleep-disordered breathing. *Sleep*, 1997, 20: 160-167.

Rothman, K. J. *Epidemiology, an introduction*. Oxford University Press, Inc., 2002.

Rowley, J. A., Aboussouan, L. S. and Badr, M. S. The use of clinical prediction formulas in the evaluation of obstructive sleep apnea. *Sleep*, 2000, 23: 929-938.

Rund, B. R., Sundet, K., Asbjornsen, A., Egeland, J., Landro, N. I., Lund, A., Roness, A., Stordal, K. I. and Hugdahl, K. Neuropsychological test profiles in schizophrenia and non-psychotic depression. *Acta Psychiatr. Scand.*, 2006, 113: 350-359.

Saboisky, J. P., Chamberlin, N. L. and Malhotra, A. Potential therapeutic targets in obstructive sleep apnoea. *Expert. Opin. Ther. Targets.*, 2009, 13: 795-809.

Saunamaki, T., Himanen, S. L., Polo, O. and Jehkonen, M. Executive dysfunction in patients with obstructive sleep apnea syndrome. *Eur. Neurol.*, 2009, 62: 237-242.

Saunamaki, T. and Jehkonen, M. A review of executive functions in obstructive sleep apnea syndrome. *Acta Neurologica Scandinavica. 115(1):1-11,* 2007a.

Saunamaki, T. and Jehkonen, M. Depression and anxiety in obstructive sleep apnea syndrome: a review. *Acta Neurol. Scand.*, 2007b, 116: 277-288.

Schmidt, M. *Rey Auditory and Verbal Learning Test. A handbook.* Los Angeles: Western Psychological Services., 1996.

Sert Kuniyoshi, F. H., Zellmer, M. R., Calvin, A. D., Lopez-Jimenez, F., Albuquerque, F. N., van der Walt, C., Trombetta, I. C., Caples, S. M., Shamsuzzaman, A. S., Bukartyk, J., Konecny, T., Gami, A. S., Kara, T. and Somers, V. K. Diagnostic accuracy of the Berlin Questionnaire in detecting sleep-disordered breathing in patients with a recent myocardial infarction. *Chest*, 2011, 140: 1192-1197.

Sharafkhaneh, A., Giray, N., Richardson, P., Young, T. and Hirshkowitz, M. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep*, 2005, 28: 1405-1411.

Sharma, S. K., Vasudev, C., Sinha, S., Banga, A., Pandey, R. M. and Handa, K. K. Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome. *Indian J. Med. Res.*, 2006, 124: 281-290.

Shepherd, K. L., James, A. L., Musk, A. W., Hunter, M. L., Hillman, D. R. and Eastwood, P. R. Gastro-oesophageal reflux symptoms are related to the presence and severity of obstructive sleep apnoea. *J. Sleep Res.*, 2011, 20: 241-249.

Shneerson, J. and Wright, J. Lifestyle modification for obstructive sleep apnoea. *Shneerson. J. , Wright. J. Lifestyle. modification. for. obstructive. sleep apnoea. The. Cochrane. Database. of Systematic. Reviews. : Reviews. 2001. Issue. 1 John. Wiley. & Sons. , Ltd. Chichester, UK DOI. : 10. 1002. /14651858. CD002875.*, 2001.

Singh, H., Pollock, R., Uhanova, J., Kryger, M., Hawkins, K. and Minuk, G. Y. Symptoms of obstructive sleep apnea in patients with nonalcoholic fatty liver disease. *Dig. Dis. Sci.*, 2005, 50: 2338-2343.

Sivertsen, B., Overland, S., Glozier, N., Bjorvatn, B., Maeland, J. G. and Mykletun, A. The effect of OSAS on sick leave and work disability. *Eur. Respir. J.*, 2008, 32: 1497-1503.

Somers, V. K., White, D. P., Amin, R., Abraham, W. T., Costa, F., Culebras, A., Daniels, S., Floras, J. S., Hunt, C. E., Olson, L. J., Pickering, T. G., Russell, R., Woo, M. and Young, T. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*, 2008, 118: 1080-1111.

Stepnowsky, C. J., Jr., Orr, W. C. and Davidson, T. M. Nightly variability of sleep-disordered breathing measured over 3 nights. *Otolaryngol. Head Neck Surg.*, 2004, 131: 837-843.

Szentkiralyi, A., Czira, M. E., Molnar, M. Z., Kovesdy, C. P., Remport, A., Szeifert, L., Vamos, E. P., Juhasz, J., Turanyi, C. Z., Mucsi, I. and Novak, M. High risk of obstructive sleep apnea is a risk factor of death censored graft loss in kidney transplant recipients: an observational cohort study. *Sleep Med.*, 2011, 12: 267-273.

Telakivi, T., Kajaste, S., Partinen, M., Koskenvuo, M., Salmi, T. and Kaprio, J. Cognitive function in middle-aged snorers and controls: role of excessive daytime somnolence and sleep-related hypoxic events. *Sleep*, 1988, 11: 454-462.

Thurtell, M. J., Bruce, B. B., Rye, D. B., Newman, N. J. and Biousse, V. The Berlin questionnaire screens for obstructive sleep apnea in idiopathic intracranial hypertension. *J. Neuroophthalmol.*, 2011, 31: 316-319.

Tishler, P. V., Larkin, E. K., Schluchter, M. D. and Redline, S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA*, 2003, 289: 2230-2237.

Tufik, S., Santos-Silva, R., Taddei, J. A. and Bittencourt, L. R. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med.*, 2010, 11: 441-446.

Twigg, G. L., Papaioannou, I., Jackson, M., Ghiassi, R., Shaikh, Z., Jaye, J., Graham, K. S., Simonds, A. K. and Morrell, M. J. Obstructive Sleep Apnoea Syndrome is Associated with Deficits in Verbal but not Visual Memory. *Am. J. Respir. Crit Care Med.*, 2010, 182: 98-103.

Vaz, A. P., Drummond, M., Mota, P. C., Severo, M., Almeida, J. and Winck, J. C. Translation of Berlin Questionnaire to Portuguese language and its application in OSA identification in a sleep disordered breathing clinic. *Rev. Port. Pneumol.*, 2011, 17: 59-65.

Verstraeten, E. and Cluydts, R. Executive control of attention in sleep apnea patients: theoretical concepts and methodological considerations. *Sleep Med. Rev.*, 2004, 8: 257-267.

Verstraeten, E., Cluydts, R., Pevernagie, D. and Hoffmann, G. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. *Sleep*, 2004, 27: 685-693.

W.G.Cochran *Sampling Techniques* . *Wiley*, New York, NY, 1963 (Second edition).

Weinreich, G., Plein, K., Teschler, T., Resler, J. and Teschler, H. [Is the Berlin questionnaire an appropriate diagnostic tool for sleep medicine in pneumological rehabilitation?]. *Pneumologie*, 2006, 60: 737-742.

White, D. P. Pathogenesis of obstructive and central sleep apnea. [Review] [87 refs]. *American Journal of Respiratory & Critical Care Medicine. 172(11):1363-70,* 2005.

White, J., Cates, C. and Wright, J. Continuous positive airways pressure for obstructive sleep apnoea. *White. J. , Cates. C. , Wright. J. Continuous. positive. airways. pressure. for. obstructive. sleep apnoea. The. Cochrane. Database. of Systematic. Reviews. : Reviews. 2001. Issue. 4 John. Wiley. & Sons. , Ltd. Chichester, UK DOI. : 10. 1002. /14651858. CD001106.*, 2001.

Wittchen, H. U. and Jacobi, F. Size and burden of mental disorders in Europe--a critical review and appraisal of 27 studies. *Eur. Neuropsychopharmacol.*, 2005, 15: 357-376.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., Van, O. J., Preisig, M., Salvador-Carulla, L., Simon, R. and Steinhausen, H. C. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur. Neuropsychopharmacol.*, 2011, 21: 655-679.

Yaggi, H. K., Concato, J., Kernan, W. N., Lichtman, J. H., Brass, L. M. and Mohsenin, V. Obstructive sleep apnea as a risk factor for stroke and death. *N. Engl. J. Med.*, 2005, 353: 2034-2041.

Young, T. Rationale, design and findings from the Wisconsin Sleep Cohort Study: Toward understanding the total societal burden of sleep disordered breathing. *Sleep Med. Clin.*, 2009, 4: 37-46.

Young, T., Evans, L., Finn, L. and Palta, M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep*, 1997, 20: 705-706.

Young, T., Finn, L., Peppard, P. E., Szklo-Coxe, M., Austin, D., Nieto, F. J., Stubbs, R. and Hla, K. M. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*, 2008, 31: 1071-1078.

Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S. and Badr, S. The occurrence of sleep-disordered breathing among middle-aged adults. *N. Engl. J. Med.*, 1993, 328: 1230-1235.

Young, T., Peppard, P. E. and Gottlieb, D. J. Epidemiology of obstructive sleep apnea: a population health perspective. *Am. J. Respir. Crit Care Med.*, 2002a, 165: 1217-1239.

Young, T., Shahar, E., Nieto, F. J., Redline, S., Newman, A. B., Gottlieb, D. J., Walsleben, J. A., Finn, L., Enright, P. and Samet, J. M. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch. Intern. Med.*, 2002b, 162: 893-900.

9.0.0 Appendices

Appendix 1: DSM IV criteria for major depression

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do note include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Appendix 2: DSM-IV criteria for anxiety disorders

Generalized Anxiety Disorder

1. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least six months, about a number of events or activities (such as work or school performance).
2. The person finds it difficult to control the worry.
3. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). Note: Only one item is required in children.
    1. restlessness or feeling keyed up or on edge
    2. being easily fatigued
    3. irritability
    4. muscle tension
    5. difficulty falling or staying asleep, or restless unsatisfying sleep
    6. difficulty concentrating or the mind going blank

Symptoms can also include nausea, vomiting, and chronic stomach aches.

1. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being away from home or close relatives (as in Separation Anxiety Disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during post-traumatic stress disorder.
2. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
3. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder.

Panic disorder with (or without) agoraphobia:

A. Both (1) and (2):

1. recurrent unexpected panic attacks
2. at least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:

- persistent concern about having additional attacks
- worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
- significant change in behavior related to the attacks

B. The presence (or absence) of agoraphobia
C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism).
D. The panic attacks are not better accounted for by another mental disorder, such as social phobia

(e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive-compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), post-traumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

Social Phobia (300.23)

A. A marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way (or show anxiety symptoms) that will be humiliating or embarrassing.
Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people and the anxiety must occur in peer settings, not just in interactions with adults.

B. Exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed Panic Attack. Note: In children, the anxiety may be expressed by crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.

C. The person recognizes that the fear is excessive or unreasonable. Note: In children, this feature may be absent.

D. The feared social or performance situations are avoided or else are endured with intense anxiety or distress.

E. The avoidance, anxious anticipation, or distress in the feared social or performance situation(s) interferes significantly with the person's normal routine, occupational (academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.

F. In individuals under age 18 years, the duration is at least 6 months.

G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., Panic Disorder With or Without Agoraphobia, Separation Anxiety Disorder, Body Dysmorphic Disorder, a Pervasive Developmental Disorder, or Schizoid Personality Disorder).

H. If a general medical condition or another mental disorder is present, the fear in Criterion A is unrelated to it, e.g., the fear is not of Stuttering, trembling in Parkinson's dsease, or exhibiting abnormal eating behavior in Anorexia Nervosa or Bulimia Nervosa.

Specify if: Generalized: if the fears include most social situations (also consider the additional diagnosis of Avoidant Personality Disorder)

Obsessive Compulsive Disorder

Obsessions

1. Recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and that cause marked anxiety or distress.
2. The thoughts, impulses, or images are not simply excessive worries about real-life problems.
3. The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action.
4. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind, and are not based in reality.

Compulsions

1. Repetitive behaviors or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not actually connected to the issue, or they are excessive.

In addition to these criteria, at some point during the course of the disorder, the individual must realize that his/her obsessions or compulsions are unreasonable or excessive. Moreover, the obsessions or compulsions must be time-consuming (taking up more than one hour per day), cause distress, or cause impairment in social, occupational, or school functioning.[4] OCD often causes feelings similar to those of depression.

PTSD

A. Exposure to a traumatic event
B. Persistent reexperience (e.g. flashbacks, nightmares)
C. Persistent avoidance of stimuli associated with the trauma (e.g. inability to talk about things even related to the experience, avoidance of things and discussions that trigger flashbacks and reexperiencing symptoms fear of losing control)
D. Persistent symptoms of increased arousal (e.g. difficulty falling or staying asleep, anger and hypervigilance)
E. Duration of symptoms more than 1 month
F. Significant impairment in social, occupational, or other important areas of functioning (e.g. problems with work and relationships.)

Notably, criterion A (the "stressor") consists of two parts, both of which must apply for a diagnosis of PTSD. The first (A1) requires that "the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others."

The second (A2) requires that "the person's response involved intense fear, helplessness, or horror."

Appendix 3: Descriptions of DSM-IV Somatoform disorders assessed

Hypochondriasis
Preoccupation with fears of having a serious disease based upon a misinterpretation of bodily sensations. The preoccupation exists despite assurance from a physician that the individual does not have a serious disease.

Somatoform pain disorder:
Pain which causes significant distress or impairment in functioning which cannot be fully explained by a physician. It must be judged to be related to psychological factors and cannot be better explained by another disorder.

Diagnostic criteria:

A. Pain in one or more anatomical sites is the predominant focus of the clinical presentation and is of sufficient severity to warrant clinical attention
B. The pain causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. Psychological factors are judged to have an important role in the onset, severity, exacerbation or maintenance of the pain
D. The symptom or deficit is not intentionally produced or feigned
E. The pain is not better accounted for by a Mood, Anxiety, or Psychotic Disorder and does not meet criteria for Dyspareunia

Somatization disorder
Includes a history of physical complaints prior to age 30 which occur over a period of several years. There must be a significant impairment in functioning or a history of resulting medical treatment. After appropriate assessment by a physician, there is a lack of explanation of the reported symptoms or for at least the severity of the complaints.

Appendix 4: Response rates

Age category	Female response rates	Male response rates
30	49.0	38.7
35	52.7	42.5
40	57.8	50.6
45	57.0	51.7
50	63.1	54.1
55	64.3	58.9
60	64.3	60.0
65	67.8	70.7
Total	59.0	52.4

Appendix 5: Scoring algorithm for the Berlin Questionnaire

Adapted from: Table 2 from Netzer, et al., 1999. (Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999 Oct 5;131(7):485-91).

The questionnaire consists of 3 categories related to the risk of having sleep apnea. Patients can be classified into High Risk or Low Risk based on their responses to the individual items and their overall scores in the symptom categories.

Categories and scoring:

Category 1: items 1, 2, 3, 4, 5.

Item 1: if '**Yes**', assign **1 point**

Item 2: if '**c**' or '**d**' is the response, assign **1 point**

Item 3: if '**a**' or '**b**' is the response, assign **1 point**

Item 4: if '**a**' is the response, assign **1 point**

Item 5: if '**a**' or '**b**' is the response, assign **2 points**

Add points. Category 1 is positive if the total score is 2 or more points

Category 2: items 6, 7, 8 (item 9 should be noted separately).

Item 6: if '**a**' or '**b**' is the response, assign **1 point**

Item 7: if '**a**' or '**b**' is the response, assign **1 point**

Item 8: if '**a**' is the response, assign **1 point**

Add points. Category 2 is positive if the total score is 2 or more points

Category 3 is positive if the answer to item 10 is 'Yes' OR if the BMI of the patient is greater than 30kg/m2.

(BMI must be calculated. BMI is defined as weight (kg) divided by height (m) squared, i.e., kg/m2).

High Risk: if there are 2 or more Categories where the score is positive

Low Risk: if there is only 1 or no Categories where the score is positive

Additional question: item 9 should be noted separately.

Appendix 6: The screening questionnaire

Spørreskjema om tretthet på dagtid

Spørsmålene gjelder din vanlige måte å reagere på i den senere tid. Selv om du ikke har gjort noe av dette i den siste tiden, så prøv likevel å finne ut hvordan situasjonene ville virke på deg.
Det er viktig at du besvarer hvert spørsmål så riktig som mulig.

Løpenummer: ☐☐☐

1 Hvor sannsynlig er det at du døser av eller sovner i følgende situasjoner i motsetning til kun å føle deg trett?

	ville aldri døse/sovne	en liten sjanse for å døse/sovne	moderat sjanse for å døse/sovne	stor sjanse for å døse/sovne
Sitte og lese	☐	☐	☐	☐
Se på TV	☐	☐	☐	☐
Sitte, inaktiv på et offentlig sted (f.eks. på teater eller et møte)	☐	☐	☐	☐
Som passasjer på en en-times biltur uten pause	☐	☐	☐	☐
Legge deg for å hvile om ettermiddagen hvis omstendighetene tillater det	☐	☐	☐	☐
Sitte og snakke med noen	☐	☐	☐	☐
Sitte stille etter lunsj (uten å ha inntatt alkohol)	☐	☐	☐	☐
I en bil, som har stoppet i noen få minutter i trafikken	☐	☐	☐	☐

2 Snorker du? Ja ☐ Nei ☐ Vet ikke ☐

Er snorkingen din plagsom for andre mennesker? Ja ☐ Nei ☐

Hvor høyt snorker du? Så høyt som pusting ☐ Så høyt som snakking ☐ Høyere enn snakking ☐ Veldig høyt ☐

3

	Nesten hver dag	3-4 ganger i uken	1-2 ganger i uken	1-2 ganger i måneden	Sjelden eller nesten aldri
Hvor ofte snorker du?	☐	☐	☐	☐	☐
Er du trett etter å ha sovet?	☐	☐	☐	☐	☐
Er du trett på dagtid?	☐	☐	☐	☐	☐
Hvor ofte har dine pustepauser blitt lagt merke til?	☐	☐	☐	☐	☐
Hvor ofte er du plaget av gjentatte oppvåkninger under søvn?	☐	☐	☐	☐	☐
Har du konsentrasjonsproblemer?	☐	☐	☐	☐	☐
Har du følt deg deprimert eller har hatt mindre interesse for å delta i aktiviteter du vanligvis har glede av?	☐	☐	☐	☐	☐

4 Hvor mange timer sover du i gjennomsnitt? Om natten ☐☐ t ☐☐ min På dagtid ☐☐ t ☐☐ min

5 Hva er din høyde og vekt? Høyde: ☐☐☐ cm Vekt: ☐☐☐ kg

Har vekten din forandret seg? Den har økt ☐ Den er redusert ☐ Ingen forandring ☐

Har du noen gang falt i søvn under bilkjøring? Ja ☐ Nei ☐

Har du tidligere mottatt behandling for søvnsykdom? Ja ☐ Nei ☐

Hvis ja, hva slags behandling? (1 eller flere kryss) ☐ Operert i svelg ☐ Vektreduksjon ☐ Operert i nesen ☐ Sovemedisin ☐ Operert bort mandler ☐ Pustemaske (CPAP) ☐ Annet

Har du noensinne hatt migrene? Ja ☐ Nei ☐

Hvor mange dager har du hatt hodepine i løpet av det siste året? ingen hodepine ☐ 1 - 11 dager ☐ 12 - 30 dager ☐ 31 - 84 dager ☐ 85 - 179 dager ☐ 180 dager eller mer ☐

6 Hvor mange sigaretter røyker du vanligvis daglig? Antall sigaretter: ☐☐☐ pr. dag

Har du hatt gjentatte ørebetennelser som barn ? Ja ☐ Nei ☐

Hvis ja, fikk du stukket hull på trommehinnen, "dren" i øret eller fjernet den falske mandelen/polypp? Ja ☐ Nei ☐

Har du hatt: Hjerteinfarkt ? Ja ☐ Nei ☐ Hjerneslag (drypp)? Ja ☐ Nei ☐

Har du / har du hatt: angina pectoris (hjertekrampe)? Ja ☐ Nei ☐ Astma? Ja ☐ Nei ☐ Allergi? Ja ☐ Nei ☐

Har du høyt blodtrykk? Ja ☐ Nei ☐ Vet ikke ☐ Har du diabetes (sukkersyke)? Ja ☐ Nei ☐

I tilfelle vi må kontakte deg med supplerende spørsmål, vennligst oppgi ditt telefonnummer:

Privat: ☐☐☐☐☐☐☐☐ Mobil: ☐☐☐☐☐☐☐☐

AHUS-skjema 7582212311

Appendix 7: The Beck Depression Inventory

I dette spørreskjemaet vil du finne setninger inndelt i grupper. Vennligst les alle setningene innenfor hver gruppe nøye. Deretter velger du den setningen i hver gruppe som best beskriver hvordan du har følt deg DEN SISTE UKA, I DAG INKLUDERT. Du kan krysse av på flere alternativer innenfor samme gruppe.

Husk å lese alle setningene innenfor en gruppe før du velger, og pass på at du gir svar innenfor alle gruppene.

A
- ❑ Jeg føler meg ikke trist
- ❑ Jeg er lei meg eller føler meg trist
- ❑ Jeg er lei meg eller trist hele tiden og kan ikke komme ut av denne tilstand
- ❑ Jeg er så trist og ulykkelig at jeg ikke holder det ut

B
- ❑ Jeg er ikke særlig pessimistisk eller motløs overfor fremtiden
- ❑ Jeg føler meg motløs overfor fremtiden
- ❑ Jeg føler at jeg ikke har noe å se frem til
- ❑ Jeg føler at fremtiden er håpløs og at forholdene ikke kan bedre seg

C
- ❑ Jeg føler meg ikke som et mislykket menneske
- ❑ Jeg føler at jeg har mislyktes mer enn andre mennesker
- ❑ Når jeg ser tilbake på livet mitt, ser jeg ikke annet enn mislykkethet
- ❑ Jeg føler at jeg har mislykkes fullstendig som menneske

D
- ❑ Jeg får like mye tilfredsstillelse ut av ting som før
- ❑ Jeg nyter ikke ting på samme måte som før
- ❑ Jeg får ikke ordentlig tilfredsstillelse ut av noe lenger
- ❑ Jeg er misfornøyd eller kjeder meg med alt

E
- ❑ Jeg føler meg ikke særlig skyldbetynget
- ❑ Jeg føler meg skyldbetinget en god del av tiden
- ❑ Jeg føler meg temmelig skyldbetynget mesteparten av tiden
- ❑ Jeg føler meg skyldbetinget hele tiden

F
- ❑ Jeg har ikke følelsen av å bli straffet
- ❑ Jeg føler at jeg kan bli straffet
- ❑ Jeg forventer å bli straffet
- ❑ Jeg føler at jeg blir straffet

G

- ❑ Jeg føler meg ikke skuffet over meg selv
- ❑ Jeg er skuffet over meg selv
- ❑ Jeg avskyr meg selv
- ❑ Jeg hater meg selv

H

- ❑ Jeg føler ikke at jeg er noe dårligere enn andre
- ❑ Jeg kritiserer meg selv for mine svakheter eller feilgrep
- ❑ Jeg bebreider meg selv hele tiden for mine feil eller mangler
- ❑ Jeg gir meg selv skylden for alt galt som skjer

I

- ❑ Jeg har ikke tanker om å ta livet mitt
- ❑ Jeg har tanker om å ta livet mitt, men jeg vil ikke omsette dem i handling
- ❑ Jeg ønsker å ta livet mitt
- ❑ Jeg ville tatt livet mitt om jeg fikk sjansen til det

J

- ❑ Jeg gråter ikke mer enn vanlig
- ❑ Jeg gråter mer nå enn jeg gjorde før
- ❑ Jeg gråter hele tiden nå
- ❑ Jeg pleide å kunne gråte, men nå kan jeg ikke gråte selv om jeg gjerne vil

K

- ❑ Jeg er ikke mer irritert nå enn ellers
- ❑ Jeg blir lettere ergerlig eller irritert enn før
- ❑ Jeg føler meg irritert hele tiden nå
- ❑ Jeg blir ikke irritert i det hele tatt over ting som pleide å irritere meg

L

- ❑ Jeg har ikke mistet interessen for andre mennesker
- ❑ Jeg er mindre interessert i andre mennesker enn jeg pleide å være
- ❑ Jeg har mistet det meste av min interesse for andre mennesker
- ❑ Jeg har mistet all interesse for andre mennesker

M

- ❑ Jeg tar avgjørelser omtrent like lett som jeg alltid har gjort
- ❑ Jeg forsøker å utsette det å ta avgjørelser mer enn tidligere
- ❑ Jeg har større vanskeligheter med å ta avgjørelser enn før
- ❑ Jeg klarer ikke å ta avgjørelser i det hele tatt lenger

N

- ❑ Jeg føler ikke at jeg ser dårligere ut enn jeg pleide å gjøre
- ❑ Jeg er redd for at jeg ser gammel eller lite tiltrekkende ut
- ❑ Jeg føler at det er varige forandringer i mitt utseende som får meg til å se lite tiltrekkende ut
- ❑ Jeg tror at jeg ser stygg ut

O

- ❑ Jeg kan arbeide omtrent like godt som før
- ❑ Det kreves ekstra anstrengelse for å ta fatt på noe
- ❑ Jeg må presse meg hardt for å gjøre noe
- ❑ Jeg klarer ikke å gjøre noe arbeid i det hele tatt

P

- ❑ Jeg sover like godt som ellers
- ❑ Jeg sover ikke så godt som før
- ❑ Jeg våkner 1-2 timer tidligere enn ellers og har vanskelig for å sovne igjen
- ❑ Jeg våkner flere timer tidligere enn jeg pleide og får ikke sove igjen

Q

- ❑ Jeg blir ikke fortere trett enn ellers
- ❑ Jeg blir fortere trett enn ellers
- ❑ Nesten alt jeg gjør blir jeg trett av
- ❑ Jeg er for trett til å gjøre noe som helst

R

- ❑ Matlysten min er ikke dårligere enn ellers
- ❑ Matlysten er ikke så god som den var før
- ❑ Matlysten min er mye dårligere nå
- ❑ Jeg har ikke mye matlyst i det hele tatt lenger

S

- ❑ Jeg har ikke gått ned meget i vekt, om i det hele tatt noe, i den senere tid
- ❑ Jeg har tatt av mer enn 2 kg
- ❑ Jeg har tatt av mer enn 4 kg
- ❑ Jeg har tatt av mer enn 6 kg

T

- ❑ Jeg er ikke mer bekymret for helsen min enn vanlig
- ❑ Jeg er bekymret over fysiske plager som verking og smerter; eller urolig mage, eller forstoppelse
- ❑ Jeg er meget bekymret over fysiske plager, og det er vanskelig å tenke på stort annet
- ❑ Jeg er så bekymret over mine fysiske plager, at jeg ikke klarer å tenke på noe annet

U

- ❑ Jeg har ikke merket noen forandring i mine seksuelle interesser i det siste
- ❑ Jeg er mindre interessert i sex enn jeg var før
- ❑ Jeg er mye mindre interessert i sex nå
- ❑ Jeg har helt mistet interessen for sex

Appendix 8: Online supplement to paper I

Estimated screening properties of the Berlin Questionnaire (BQ) and prevalences of Obstructive Sleep Apnea (OSA)

The data sample for the clinical phase consisted of 518 subjects: 153 in the BQ low-risk group and 365 in the BQ high-risk group. We assumed that the BQ high risk group, which was randomly drawn from screening-phase subjects, was representative of BQ high risk subjects in the screening sample. However, empirical analyses showed that the BQ low risk group group of 153 subjects would result in biased estimates because of exclusion of 5541 questionnaires with missing BQ values. Therefore, we first calculated pretest probabilities for each stratum of the BQ high risk and BQ low risk groups separately. Second, the resulting stratum-specific BQ high risk and BQ low risk estimates were combined using weighted averages.

1: Prevalences of OSA in the clinical sample

Unadjusted prevalences for each stratum were estimated for the 518 subjects available. Then, weights (W_h, h being the stratum indicator) were defined as the ratio of a particular strata size in the population (N_h) to the total of the population (N), i.e., $W_h = \frac{N_h}{N}$. A weighted pretest probability was calculated for each stratum as suggested by Cochran (W.G.Cochran 1963): $prev = \sum_h W_h p_h$, where p_h is the proportion of subjects with an apnea–hypopnea index (AHI) greater than the cutoff value in stratum h. The variance of the estimated $prev$ was then defined as $Var(prev) = \frac{1}{N^2} \sum_h \frac{N_h^2 (N_h - n_h)}{N_h - 1} \frac{p_h (1 - p_h)}{n_h - 1}$, where n_h is the number of sampled subjects in stratum h.

2: Adjustment for participation status in the statistical sample

Stratum-specific pretest probabilities were adjusted for participation status based on the remaining 1254 subjects drawn but not included in the clinical sample using a logistic regression model. On the basis of the 518 cases included in the clinical sample of the study, we fitted a logistic regression model for AHI cutoff values of 5 and 15. Items from the BQ, items assessing comorbidity and dummy variables for each stratum were considered. Because of too many

missing values or high p-values in univariate analyses, only the BQ snoring category variable, obesity, defined as a body mass index > 30, self-reported hypertension and strata dummies were left in the final multivariate logistic regression model. According to standard diagnostic tests, the model was of good quality. Therefore, we used the model to predict the probability of an AHI above the cutoff value for subjects that were drawn but not included in the clinical phase. As the estimated probabilities within each stratum were rather homogeneous as indicated by a low variance, they were grouped by averaging them separately for each stratum. These averaged probabilities were then used as estimates for prevalences for all 1772 subjects drawn and were weighted using the previously defined strata weights.

To evaluate the reliability of the regression model, we first compared observed and estimated crude prevalences for OSA defined by the AHI cut-off values using a sample of 518. Estimated prevalences were nearly identical to the observed data for each stratum, indicating that the model predicted well within the study sample. As the same model was intended to be used for extrapolating the estimates for the estimation sample of the study, we also simulated the probability of an AHI above the cut off for different strata with the assumption that the estimated regression model was correct. The simulated prevalences, calculated from 100 iterations, were also nearly identical to the observed prevalences and consequently, the estimated prevalences in each stratum for the 518 subjects. The 100 iterations were then used to estimate the screening properties of the BQ. As the explanatory variables preserved the form of the corresponding distributions for subjects drawn but not included in the clinical phase, we concluded that the same regression model could also be used to predict prevalences and screening properties when extrapolating the results to the screening sample.

Prevalences for subjects drawn and included in the clinical sample and for subjects drawn and not included in the clinical sample were combined by calculating a weighted average for these two groups separately for each stratum. Weights were defined by strata sizes for each group. The adjustment for bias in the BQ low risk group was performed in the same manner using the estimated probabilities.

The final estimates of screening properties of the BQ and prevalences of OSA in the general population were obtained using the formula presented above and are presented in table 3-4 in the main article. Comprehensive estimates of BQ screening properties are presented in table E1.

Table E1: Final estimates of screening properties of the BQ

AHI5 (area under the receiver operater curve for the model = 0.87)

	Empirical – 518	**Simulated – 518**	**Simulated – 14,687***
Sensitivity	79.4	79.7	37.2 (36.0–38.4)
Specificity	40.5	40.8	84.0 (83.2–84.7)
PPV	62.2	62.1	61.3 (59.7–62.9)
NPV	61.4	62.3	66.2 (65.3–67.1)
LR+	1.3	1.4	2.32 (2.19–2.46)
LR-	0.5	0.5	0.75 (0.73–0.76)
OR	2.6	2.8	3.1 (2.9–3.4)

AHI15 (area under the receiver operater curve for the model = 0.74)

	Empirical – 518	**Simulated – 518**	**Simulated – 14,687***
Sensitivity	82.8	83.1	43.0 (41.2–44.8)
Specificity	34.9	35.0	79.7 (79.0–80.5)
PPV	35.6	35.5	33.5 (32.0–35.0)
NPV	82.4	82.8	85.5 (84.8–86.1)
LR+	1.3	1.3	2.12 (2.01–2.25)
LR-	0.5	0.5	0.72 (0.69–0.74)
OR	2.6	2.8	3.0 (2.7–3.2)

AHI = apnea–hypopnea index

*The simulated screening sample consisted of 14.687 subjects consisting of the 9319 subjects eligible for the clinical sample plus the 5671 BQ low risk subjects with missing BQ items minus 173 subjects with missing variables used in the model.

Appendix 9: Online supplement from paper III

Sleep apnoea, anxiety, depression and somatoform pain: A community-based high risk sample
Supplementary material

TABLE S1. Prevalence of current psychiatric disorders and differences between participants with and without obstructive sleep apnoea (apnoea hypopnoea index ≥ 15) by chi-square test (N = 289)

	OSA N = 104	**No OSA N =185**	***P*-value**
Affective disorders			
Major depressive disorder	**8 (7.7)**	**27 (14.6)**	**0.089**
Dysthymia	3 (2.9)	2 (1.1)	0.355[a]
Current affective disorder	10 (9.6)	29 (15.7)	0.148
Anxiety disorders			
Current panic disorder	5 (4.8)	12 (6.5)	0.560
Agoraphobia without panic disorder	1 (1.0)	1 (0.5)	1.000[a]
Social phobia	5 (4.8)	8 (4.3)	1.000[a]
Obsessive–compulsive disorder	1 (1.0)	4 (2.2)	0.657[a]
Post-traumatic stress disorder	3 (2.9)	13 (7.0)	0.139
Generalised anxiety disorder	5 (4.8)	9 (4.9)	0.983
Current anxiety	**13 (12.5)**	**30 (16.2)**	**0.394**
Alcohol and substance abuse			
Current alcohol abuse	2 (1.9)	3 (1.6)	1.000[a]
Somatoform disorders			
Hypochondriasis	1 (1.0)	2 (1.1)	1.000[a]
Somatoform pain disorder	**16 (15.4)**	**40 (21.6)**	**0.198**
Somatisation disorder	2 (1.9)	7 (3.8)	0.497[a]
Current somatoform disorder	17 (16.3)	41 (22.2)	0.236
Any psychiatric disorder[b]	33 (31.7)	76 (41.1)	0.115

Results are presented as number and percent of participants with disorder(s).
a = Fisher's exact test
Interrater reliability was tested for disorders written in bold.
b = Any one or more of the psychiatric disorders listed in the table

TABLE S2. Prevalence of current psychiatric disorders and differences between participants with and without obstructive sleep apnoea (apnoea hypopnoea index ≥ 30) by chi-square test (N = 289)

	OSA N = 56	**No OSA N =233**	***P*-value**
Affective disorders			
Major depressive disorder	**5 (8.9)**	**30 (12.9)**	**0.416**
Dysthymia	1 (1.8)	4 (1.7)	1.000[a]
Current affective disorder	6 (10.7)	33 (14.2)	0.498
Anxiety disorders			
Current panic disorder	2 (3.6)	15 (6.4)	0.541[a]
Agoraphobia without panic disorder	0 (0.0)	2 (0.9)	1.000[a]
Social phobia	4 (7.1)	9 (3.9)	0.287[a]
Obsessive–compulsive disorder	1 (1.8)	4 (1.7)	1.000[a]
Post-traumatic stress disorder	0 (0.0)	16 (6.9)	0.048[a]
Generalised anxiety disorder	0 (0.0)	14 (6.0)	0.080[a]
Current anxiety	**6 (10.7)**	**37 (15.9)**	**0.329**
Alcohol and substance abuse			
Current alcohol abuse	1 (1.8)	4 (1.7)	1.000[a]
Somatoform disorders			
Hypochondriasis	0 (0.0)	3 (1.3)	1.000[a]
Somatoform pain disorder	**8 (14.3)**	**48 (20.6)**	**0.283**
Somatisation disorder	1 (1.8)	8 (3.4)	1.000[a]
Current somatoform disorder	8 (14.3)	50 (21.5)	0.229
Any psychiatric disorder[b]	17 (30.4)	92 (39.5)	0.206

Results are presented as number and percent of participants with disorder(s).
a = Fisher's exact test
Interrater reliability was tested for disorders written in bold.
b = Any one or more of the psychiatric disorders listed in the table

Papers

I

II

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ORIGINAL ARTICLE

Obstructive sleep apnea, verbal memory, and executive function in a community-based high-risk population identified by the Berlin Questionnaire Akershus Sleep Apnea Project

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Abstract
Purpose Cognitive functions in community-dwelling adults at high risk of obstructive sleep apnea have not been described and nor are associations between cognitive functions and obstructive sleep apnea severity fully understood. The study aimed to describe verbal memory and executive function in community-dwelling adults identified by the Berlin Questionnaire and to investigate associations between these cognitive domains and different obstructive sleep apnea severity indicators.

Methods Among 29,258 age- and gender-stratified persons 30–65 years who received the Berlin Questionnaire by mail, 16,302 (55.7%) responded. From 654 randomly drawn respondents with BQ high risk who were approached for study participation, 290 participants (55.9% males, mean age 48.2 years) were included. Verbal memory was assessed by Rey Auditory Verbal Learning Test and executive function by Stroop test. Obstructive sleep apnea severity indicators were assessed by polysomnography.

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Results Mean (standard deviation) verbal learning score was 42.0 (8.9), mean interference time was 31.1 (12.7), median (25th percentile, 75th percentile) apnea–hypopnea index was 7.7 (2.4–22.2), and mean average oxygen saturation was 94.3 (2.0). Verbal learning score was independently associated with average oxygen saturation (β=0.721, p=0.025) in multivariate linear regression models adjusted for putative confounders. Interference time was only related to OSA severity indicators in bivariate analyses.

Conclusions Verbal memory and executive function impairments were mild in community-dwelling adults at high risk of obstructive sleep apnea. Average oxygen saturation was the indicator of obstructive sleep apnea severity most strongly associated with cognitive function.

Keywords Neurobehavioural manifestations · Polysomnography · Epidemiology · Sleep apnea syndromes · Sleep disordered breathing

Introduction

The association between moderate to severe obstructive sleep apnea (OSA) and impaired neurocognitive function is well-established [1–6]. It is unclear whether this association is related to intermittent oxygen desaturations or the repeated arousals of OSA [1–6]. Neurocognitive function consists of basal processes (i.e., attention, motor speed, and vigilance) and more differentiated cognitive functions, of which impairments in verbal memory [7, 8] and executive functioning [9–11] have been found to be most strongly related to OSA. However, findings of cognitive impairments in patients with moderate to severe OSA have not been consistently reproduced in community-based studies.

We identified seven community-based studies [12–18] and two studies of mild OSA in volunteers [19, 20] that assessed cognitive function with rater-administered instruments in addition to objective sleep measures. Four studies reported associations between OSA and at least one cognitive domain [13, 14, 19, 20]. Affected cognitive domains were verbal memory (Wechsler Memory Scale [13], declarative memory factor [20]), and working memory (composite factor [20]), spatial orientation (Clock Test [13]), executive function (Wechsler Adult Intelligence Scale-Revised Digits Backward Subtest [19]), and cerebral efficiency (composite factor [14]).

Five of the identified studies reported analyses by variables assessing oxygen saturation (4% oxygen desaturation index, lowest oxygen saturation, or percentage time below 90% oxygen saturation [13, 16–18, 20]). In all these studies, the associations with oxygen saturation were at least as strong as the associations reported between cognitive functions and apnea–hypopnea indices (AHIs). The average oxygen saturation during sleep has recently been associated with cerebrovascular regulation in community-dwelling adults [21]. None of the identified community-based studies reported analyses by the arousal index.

In addition to the question of which mechanisms of OSA are associated with cognitive impairment, the relative importance of sociodemography and other potential health-related factors, such as alcohol abuse, sleepiness, use of hypnosedatives, smoking, and asthma [15–17, 19, 20], are not fully understood. The present study is unique in terms of including a large, community-based sample of participants identified by the Berlin Questionnaire (BQ) [22] as being at risk of OSA. The BQ is a widely used screening tool for OSA that has been used as a proxy for OSA diagnosis in nationwide US telephone surveys [23, 24] and validated in the Norwegian general population [25]. We are not aware of any study of cognitive function in a strictly defined probability sample of OSA. We aimed to (1) characterize cognitive function among community-based, BQ high-risk participants; and (2) investigate associations between verbal memory, executive function, and OSA severity as assessed by the AHI, indicators of oxygen saturation, and the arousal index before and after adjustment for putative confounders such as age, gender, comorbid conditions (alcohol abuse, asthma), use of hypnosedatives, sleepiness, smoking, and educational level. We hypothesized that verbal memory and executive function would be more closely related to variables assessing oxygen saturation than the AHI or the arousal index.

Materials and methods

Participants

The study population consisted of 29,258 persons (aged 30–65 years, 50% female) of whom 16,302 (55.7%) completed the BQ [22] (Fig. 1). Of them, 3,960 (24.3%) were classified at risk of OSA according to the BQ scoring algorithm [26], which defines three risk categories: (I) snoring, (II) daytime somnolence, and (III) obesity or self-reported hypertension (Table 1). Obesity was defined as a body mass index (BMI) >30 kg/m^2 calculated from self-reported weight and height. High risk on the BQ was defined as any combination of two or three of these categories [26].

From the 3,960 BQ high-risk persons classified at risk for OSA, 1,085 (27.4%) were randomly drawn and 852 of them were asked to participate in the Akershus Sleep Apnea Project (ASAP) for clinical investigations. Persons with established cardiovascular disease, diabetes, or previous otitis media surgery were oversampled. The reason that not all 1,085 were asked to participate was that, after the

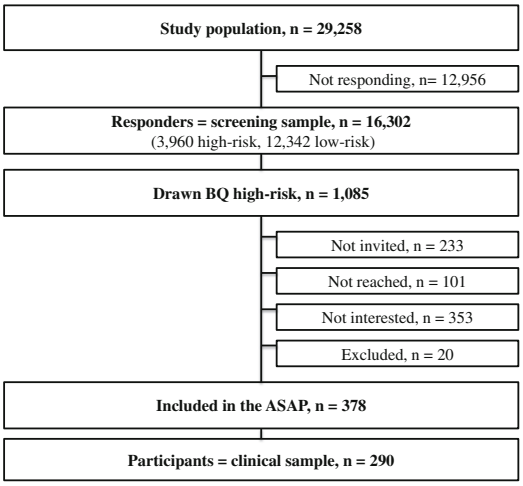

Fig. 1 Diagram to show the flow of persons from the study population to the final inclusion of participants

predefined strata were saturated, the invitation process was stopped. Altogether, 101 persons were not reached by telephone after three attempts; 353 declined participation; 233 not approached, and 20 were excluded according to the following exclusion criteria: use of continuous positive airway pressure (n=10), pregnancy (n=4), inadequate Norwegian language skills (n=4), and severe physical impairment as defined by inability to walk the stairs of our sleep laboratory (n=2). This recruitment procedure resulted in 378 participants which was 44.3% from 852. The present sample comprises consecutive, BQ high-risk persons included in the ASAP between 1 June 2006 and 31 March 2007. During this time, 654 persons had been approached and 290 participants (44.3%) were included.

Measures

Cognitive function

The Rey Auditory Verbal Listening Test (RAVLT) [27] was used to assess verbal memory. The RAVLT score, which is the sum of words retrieved from hearing 15 common words five times (range, 0–75), was calculated.

A shortened version of the Comali/Kaplan Stroop test [28] was used to assess response inhibition, which is regarded as a measure of executive function. The score computed was Stroop interference time, the time used on a task requiring response inhibition minus the average time used to name 48 colored patches and to read 48 color

Table 1 Description of the screening sample and the clinical sample

	Screening sample n=3,960	Participants n=290	p Value
Age in years, mean (SD)	48.8 (10.3)	48.2 (11.2)	0.357
Male gender, n (%)	2,198 (55.5)	162 (55.9)	0.899
Higher education, n (%)		80 (28.1)	
Body mass index, mean (SD)	29.1 (5.2)	29.0 (4.9)	0.951
Smoking, n (%)		89 (31.0)	
Alcohol abuse, n (%)		5 (1.7)	
Berlin Questionnaire			
Snoring category, n (%)	3,654 (92.3)	264 (91.0)	0.412
Daytime somnolence category, n (%)	2,498 (63.1)	205 (70.7)	0.005
Hypertension/obesity category, n (%)	2,624 (66.3)	193 (66.6)	0.914
Sleepiness and comorbidities			
Epworth Sleepiness Scale, mean (SD)	8.8 (4.5)	9.5 (4.2)	<0.001
Excessive daytime sleepiness, n (%)	1,336 (33.7)	117 (40.9)	<0.001
Self-reported asthma, n (%)	597 (16.5)	50.0 (18.8)	0.289
Polysomnography indices			
AHI, median (25th and 75th percentiles)		7.7 (2.4, 22.2)	
Arousal index, mean (SD)		19.9 (15.9)	
Nadir oxygen saturation, median (25th and 75th percentiles)		86.0 (82.0, 89.0)	
Average oxygen saturation, mean (SD)		94.3 (2.0)	
Relevant standard blood tests			
Blood hemoglobin[a], mean (SD)		15.1 (1.2)	
Serum ferritin[b], mean (SD)		121.5 (96.0)	

AHI apnea–hypopnea index, *SD* standard deviation

[a] Gram/deciliter

[b] Microgram/liter

names. Thus, a low score (seconds) indicates better executive function.

All assessments were made by the first author (HHS) before sleep registering.

Sleep recordings

Participants underwent in-hospital polysomnography, including two-channel electroencephalography (C4/A1 and C3/A2), two-channel electrooculography, one-channel submental electromyography, leg electromyography (tibialis), measurement of oxygen saturation by finger plethysmography (Nonin, Plymouth, MN, USA), assessment of breathing movements (Respitrace; Ambulatory Monitoring, Ardsley, NY, USA), nasal and oral air flow assessment (Protech, Woodinville, WA, USA), and body position monitoring. All electrophysiological signals were preamplified, stored and subsequently scored at 30-s epochs using the Somnologica 3.2 software package (Flaga-Medcare, Buffalo, NY, USA) in accordance with the Rechtshaffen and Kales scoring manual [29] by two US board-certified polysomnography technicians who were blinded to the result of the BQ. Apneas were scored when airflow dropped below 10% of the reference amplitude for more than 10 s. Hypopneas were scored when airflow dropped below 70% for more than 10 s with a subsequent oxygen desaturation of 4%. Arousals were documented and classified according to standard criteria [30]. The AHI and arousal indices were calculated as the sum of apneas plus hypopneas and the sum of arousals per hours of sleep, respectively. The following variables of oxygen saturation were registered: the 4% oxygen desaturation index (4% ODI) [13], percent time <90% saturation [16, 20], nadir oxygen saturation [20], and average oxygen saturation during sleep [21].

Demographic and clinical characteristics

Demographic data, BQ categories, sleepiness, and medical comorbidities were reported in the screening questionnaire 3–11 months prior to the overnight stay (Table 1). Educational level and smoking were reported during the overnight stay. Higher education was defined as having any college or university degree. A dichotomous variable of current smoking was computed, based on reported daily smoking. Missing information was replaced when possible by answers to other items assessing smoking. Diagnoses of alcohol abuse and/or dependency were determined by the structured clinical interview for Diagnostic and Statistical Manual for Mental Disorders [31] administered by the first author after measurement of cognitive function. The presence of asthma was assessed by self-report (yes/no) in the screening questionnaire. Sleepiness was assessed by a Norwegian translation of the Epworth Sleepiness Scale (ESS) [32, 33]. Excessive daytime sleepiness (EDS) was defined as a score >10 on the ESS. Blood hemoglobin and serum ferritin were analyzed from blood samples obtained in the morning after sleep registration.

Ethics

The study protocol was approved in 2005 by the Regional Committee for Medical Research Ethics in Eastern Norway, the National Data Inspectorate and the Norwegian Social Science Data Services. All subjects provided written consent before participating.

Statistical analyses

Differences between participants and nonparticipants included in the screening sample were analyzed by Student's *t* test and Chi-square test for normally distributed continuous variables and categorical variables, respectively. The choice of categorization of measures of OSA severity in tertiles was based on the distribution of the AHI with the upper tertile close to the clinical cut-off between mild (AHI 5–14.9) and moderate (AHI 15–29.9) OSA [34]. Differences in cognitive scores between clinical cut-off values of the AHI and these tertiles in other measures of OSA severity were analyzed by one-way ANOVA with Bonferroni post hoc test. Two-sided P values<0.05 were considered statistically significant. Comparisons of cognitive test results between groups of putative confounders were performed with Student's *t* test. Standard multiple regression models adjusting for age, gender and higher education were used to examine the effect of OSA severity on test results. Because of missing information regarding polysomnography data (n=1), oxygen saturation data (n=2), higher education (n=5), RAVLT (n=4), and Stroop test (n=2), the numbers of participants included in multivariate analyses declined to a minimum of 281. Non-normal variables assessing OSA severity were logarithmically transformed. Standard models were finally adjusted by adding putative confounders and strata variables one by one to these basic models. If a 15% change in the coefficient of the measure of OSA severity was observed, the variable was included in the final model. Interaction analyses and analyses of alternative distributions of measures of OSA severity were performed. All statistical analyses were obtained by using the Statistical Package for Social Sciences, version 16.0.

Results

Sociodemographic and clinical characteristics are displayed in Table 1. There were no significant differences in age, gender, snoring, obesity, or history of hypertension between the 290 participants and the 3,670 nonparticipants. However, a

significantly higher proportion of participants than non-participants were classified in the daytime somnolence category (participants 70.7%, nonparticipants 62.5%), and in the EDS category (participants 43.1%, nonparticipants 33.0%). Five persons fulfilled the diagnostic criteria for alcohol abuse/dependency.

The mean RAVLT score and Stroop interference time among all participants were 42.0 words retrieved (SD=8.9) and 31.1 s (SD=12.7), respectively. Compared with available norms [35, 36], the group performed 1.3 to 1.2 standard deviations below normal mean. Unadjusted mean cognitive test scores by commonly used cut-points for the AHI and tertiles of nadir- and average oxygen saturation are displayed in Table 2. Participants with AHI ≥15 had significantly longer mean interference times on the Stroop test than participants without OSA (p=0.001). A similar pattern with a significant loss of cognitive performance among participants in the tertile with the most severe versus mildest oxygen saturation was seen when categorized by lowest mean nadir oxygen saturation (83.0–54.0) and mean average oxygen saturation (93.8–81.8). Similar but less discriminant patterns were seen for tertiles of the 4% ODI and percent time <90% saturation (data not shown). Cognitive test scores did not differ significantly between tertiles of the arousal index (data not shown).

Bivariate differences in cognitive scores by putative confounders are displayed in Table 3. Correlation coefficients between the Stroop interference times and standard blood samples were not significant. Correlation coefficients between the RAVLT score and blood hemoglobin and serum ferritin were –0.168 (p=0.005) and –0.120 (p=0.046), respectively. The ESS was not significantly related to any of the cognitive tests (data not shown).

The final multiple regression models for the RAVLT score and Stroop interference time with average oxygen saturation as the independent variable assessing OSA severity are presented in Tables 4 and 5. Average oxygen saturation was found to be independently related to the RAVLT score but not to the Stroop test.

Neither logarithmically transformed AHI, nadir oxygen saturation, nor 4% ODI were independently related to the RAVLT score and the Stroop interference time (Online Resource, Tables 1–4). Percent time <90% was not independently related to the RAVLT score but to the Stroop interference time when adjusted for age, gender, and higher education (Online Resource, Tables 7–8). However, this association disappeared when BMI or BQ risk categories were added to the model.

Discussion

To our knowledge, this is the first study to describe verbal memory and executive function in community-dwelling

Table 2 Unadjusted mean cognitive test scores by established cut-off values of the AHI or tertiles of nadir- and average oxygen saturation

Test	Category 1 *n* (range) Mean±SD	Category 2 *n* (range) Mean±SD	Category 3 *n* (range) Mean±SD	*F* test[a] *p* Value	Trend test *p* Value
	AHI	AHI	AHI		
	111 (0.0–4.9)	70 (5.0–14.9)	104 (15.0–104.0)		
RAVLT score[b]	43.2±8.2	41.8±9.4	40.7±9.3	0.109	0.036
Stroop interference time[c]	28.4±12.0*	30.5±11.5	34.5±13.6	0.001	<0.001
	Upper tertile nadir O_2	Mid tertile nadir O_2	Lower tertile nadir O_2		
	85 (95.0%–89.0%)	110 (88.0%–84.0%)	93 (83.0%–54.0%)		
RAVLT score[b]	43.2±8.4*	42.9±8.2*	39.7±9.9	0.010	0.008
Stroop interference time[c]	29.2±12.5*	29.1±11.8*	35.5±13.0	<0.001	0.001
	Upper tertile average O_2	Mid tertile average O_2	Low tertile average O_2		
	97 (97.8%–95.3%)	93 (95.2%–93.9%)	98 (93.8%–81.8%)		
RAVLT score[b]	45.5±8.9*	41.6±8.4	38.8±9.5)	<0.001	<0.001
Stroop interference time[c]	27.2±9.7*	32.7±14.4	33.7±12.8)	<0.001	<0.001

[a] Test for overall model fit

[b] Sum of trials 1–5

[c] Difference in seconds

*p<0.05 for post hoc tests between category 1 and the two other categories identified by Bonferroni post hoc tests

AHI apnea–hypopnea index, *RAVLT* Rey Auditory Verbal Learning Test

Table 3 RAVLT score and Stroop interference time according to cofactors

	Number	RAVLT score[a] Mean±SD	*p* Value	Number	STROOP interference time[b] Mean±SD	*p* Value
Gender						
Male	161	39.8±9.1	<0.001	160	31.8±13.6	0.365
Female	125	44.6±8.0		128	30.5±11.7	
Higher education						
Yes	79	45.8±8.1	<0.001	80	28.9±11.4	0.088
No	203	40.6±8.8		203	31.7±13.0	
Smoking						
Yes	88	41.8±8.7	0.876	89	30.2±12.3	0.327
No	195	42.0±9.1			31.8±13.1	
Self-reported asthma						
Yes	48	42.1±9.9	0.905	49	33.7±14.9	0.134
No	214	42.2±8.7		216	30.6±12.5	
Use of hypnosedatives						
Yes	15	42.1±8.9	0.117	15	38.4±18.2	0.132
No	271	38.4±8.9		273	30.8±12.4	

[a] Rey Auditory Verbal Learning Test, sum of trials 1–5

[b] Difference in seconds

MI myocardial infarction

adults at high risk of having OSA, as identified by the BQ. Verbal memory was found to be independently related to average oxygen saturation, while executive function was not related to OSA severity. The AHI, which is the most commonly used measure when assessing OSA severity, was only related to cognitive function in bivariate analyses. The arousal index was not related to cognitive function in any analysis.

The recruitment of participants by the BQ in this study resulted in a sample of participants with a relatively low median AHI of 7.7 (25th percentile=2.4, 75th percentile=22.2) compared with clinical studies of OSA. However, more than one third of the sample had an AHI of ≥15, which is the criteria for moderate to severe OSA [34]. The cognitive function scores among participants were considerably higher than that reported in "mild cognitive impairment", which is the mildest clinical entity of impaired cognitive function [37]. However, the mean age of participants in this study was considerably lower than the mean age of patients with mild cognitive impairment [37]. Thus, our study adds knowledge to epidemiological factors associated with early cognitive decline rather than being a study of cognitively impaired subjects per se.

Table 4 Final model for RAVLT score fitted by age, gender, education, average oxygen saturation, and covariates

n=281 (adjusted R^2=0.199; p<0.001)[a]	β[b]	SE[c]	*p* Value
Intercept	−19.278	32.969	0.559
Gender (0=female, 1=male)	−3.251	1.033	0.002
Age[d]	−0.168	0.047	<0.001
Higher education[e]	4.722	1.076	<0.001
Average oxygen saturation	0.721	0.320	0.025
Body mass index	0.066	0.106	0.535

[a] Results from multiple regression analysis. Inclusion of the variables smoking, self-reported myocardial infarction, sleepiness, use of antidepressants, and use of hypnosedatives in the model did not affect the relationship between any covariate on the dependent variables

[b] β is the unstandardized regression coefficient of the variable

[c] SE is the standard error of β

[d] Unit of age, 5 years

[e] College or university

Studies in the last 5 years have confirmed that verbal memory is particularly affected by OSA pathology [7, 8]. On the other hand, the association between OSA and the complex executive function may be spurious [8, 11, 17] and potentially influenced by attention [5, 38]. Unfortunately, no objective measures of attention were available in the ASAP. Accordingly, the Stroop interference time test, which provides adjustment for baseline speed [5], was chosen.

We have not identified any previous studies that have reported test results from the RAVLT or the Comali/Kaplan Stroop test in community-based OSA populations. We therefore compared the RAVLT score with general population norms [35] and the Stroop interference time with an available clinical sample [36]. Both results indicate mildly impaired cognitive function. RAVLT scores are equivalent with general population norms of persons 20–30 years older than the actual age of participants of the study [35].

The salient finding of the second aim of this study was the support of our hypothesis that oxygen saturation, rather than the AHI or the arousal index, was associated with

Table 5 Model for Stroop interference time fitted by age, gender, education, average oxygen saturation and covariates

n=282 (adjusted R^2=0.223, p<0.001)[a]	β[b]	SE[c]	p Value
Intercept	35.389	48.319	0.465
Gender (0=female, 1=male)	0.105	1.507	0.944
Age[d]	0.494	0.068	<0.001
Higher education[e]	−3.047	1.551	0.051
Average oxygen saturation	−0.360	0.470	0.444
Body mass index	0.206	0.156	0.189
Self-reported asthma	2.331	1.857	0.211

[a] Results from multiple regression analysis. Inclusion of the variables smoking, logAHI, myocardial infarction, sleepiness, use of antidepressants, and use of hypnosedatives in the model did not affect the relationship between any covariate on the dependent variables

[b] β is the unstandardized regression coefficient of the variable

[c] SE is the standard error of β

[d] Unit of age, 5 years

[e] College or university

verbal learning and executive function after adjusting for age, gender, higher education, and putative confounders. Smoking, alcohol consumption, and subjective sleepiness were not related to cognitive test scores and thus were not putative confounders of the associations examined.

Regarding the AHI, the fact that cognitive test scores differed significantly by tertiles of the AHI only in bivariate analyses (Table 2) suggests that the association between AHI and cognitive function was potentially mediated by covariates included in the final multiple regression analysis. On the other hand, this is unlikely because the association between the AHI and both cognitive test scores disappeared when age, gender, and higher education, which are unlikely mediators of this association, were adjusted for. Regarding potential effect modification between the AHI and these covariates, no interaction terms were significant when added, one pair at a time, to the multivariate models of AHI and verbal memory and executive function, respectively.

Regarding oxygen saturation, a novel finding in our study was that average oxygen saturation, rather than the commonly used variables, explained most of the variation in cognitive function. The effect of average oxygen saturation has, somewhat surprisingly, not been reported in any of the eight identified previous community-based studies or studies of mild OSA [12–17]. Studies of cognitive function in clinical samples of moderate to severe OSA have reported a similar level of average oxygen saturation as our study [7, 39, 40], and a recent study also found that average oxygen saturation was an independent predictor of cognitive decline in middle-aged adults with moderate to severe OSA [41]. This finding was age-dependent.

We believe that the lack of an association between the arousal index and measures of cognitive function should be understood in relation to our finding of an independent association with oxygen saturation. Objective sleep quality has traditionally been more strongly associated with memory consolidation than hypoxia [42]. However, regarding OSA, accumulating evidence from studies applying neuroimaging techniques [43–45] and studies of animal models [46, 47] indicates that intermittent hypoxia is the most important cause of neural injury related to this disorder over time.

Finally, it should be kept in mind that different variables assessing intermittent hypoxia or oxygen saturation might be related to other aspects of chronic disease than OSA, such as the nonlinear oxygen dissociation curve, abdominal obesity limiting the functional residual capacity, or other lung diseases. It is therefore interesting that the relations between average oxygen saturation and cognitive function were not altered by the inclusion of blood hemoglobin and serum ferritin in the multivariate models. Regarding obesity, BMI only slightly altered the association between average oxygen saturation and the cognitive test results. The multiple regression model for Stroop interference time was adjusted for potential confounding by self-reported asthma. Asthma was not found to be related to the association between average oxygen saturation and the RAVLT score.

In summary, the finding of an independent association between oxygen saturation, rather than the AHI or the arousal index, with early cognitive decline in participants with high risk of OSA emphasizes that future studies should specify variables of OSA severity prior to analysis. Future studies should also include enough subjects to allow adjustment for putative confounders. Regarding which variables to assess, we argue that average oxygen saturation and other variables assessed through the whole night (4% ODI, percentage time below 90% saturation) should be considered in community-based samples or studies of mild OSA because of the advantage of being less vulnerable to artifacts than, for example, the nadir oxygen saturation.

Strengths and limitations

The use of polysomnography to assess OSA severity in a large, community-based sample is an obvious strength. However, the use of only a single, hospital-based polysomnography recording is a potential limitation of the study [48]. Therefore, the possible first night effect could not be controlled for. It remains unknown what, if any, effect it may have had on indicators of OSA severity.

Another strength of the study is that cognitive tests were performed by the same physician at identical time points the day prior to the polysomnography. Both tests were suggested by Decary et al. [2] for use in OSA patients, although the

limited number of tests increased the probability of a type 2 statistical error (i.e., finding no association when the association is truly present). The cognitive tests should ideally have been performed after the sleep studies, but with the chronic nature of OSA, we consider this to be only a minor weakness.

Regarding potential limitations, the relatively low response, and participation rates biased the sample towards including participants with more daytime impairments. However, we believe that this mechanism did not significantly affect our findings because daytime impairments did not contribute to the multivariate models displayed in Tables 4 and 5.

The multivariate models should ideally have been adjusted for diagnosed asthma rather than self-reported asthma and more putative confounders such as better measures of attention [9] or inflammation [49]. However, the statistical models in this study are adjusted for more putative confounders than most previous community-based studies of the relation between OSA and cognitive function.

Finally, the cross-sectional design and the lack of a control group were limitations to causal interpretations. The cross-sectional design also limited us from including variables in the multivariate models that assessed psychological distress because it could not be determined whether psychological distress would be a cause or a consequence of cognitive impairment.

Conclusion

Verbal memory and executive function were mildly impaired in community-dwelling adults at high risk of OSA. The data supported the hypothesis that memory decline in OSA, as measured by the RAVLT score, is more strongly related to oxygen desaturation than the AHI or the arousal index. Average oxygen saturation during sleep, rather than traditional variables assessing oxygen saturation related to OSA, was the variable that was most strongly related to the RAVLT score. No independent relations were found between executive function, as measured by the Stroop interference time, and variables of OSA severity. The effect of average oxygen saturation on cognitive function should be explored in future studies.

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References

1. Engleman H, Joffe D (1999) Neuropsychological function in obstructive sleep apnoea. Sleep Med Rev 3:59–78
2. Decary A, Rouleau I, Montplaisir J (2000) Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. Sleep 23:369–381
3. Beebe DW, Groesz L, Wells C, Nichols A, McGee K (2003) The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 26:298–307
4. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D (2004) Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc 10:772–785
5. Verstraeten E, Cluydts R (2004) Executive control of attention in sleep apnea patients: theoretical concepts and methodological considerations. Sleep Med Rev 8:257–267
6. Saunamaki T, Jehkonen M (2007) A review of executive functions in obstructive sleep apnea syndrome. Acta Neurol Scand 115(1):1–11
7. Naegele B, Launois SH, Mazza S, Feuerstein C, Pepin JL, Levy P (2006) Which memory processes are affected in patients with obstructive sleep apnea? An evaluation of 3 types of memory. Sleep 29:533–544
8. Twigg GL, Papaioannou I, Jackson M, Ghiassi R, Shaikh Z, Jaye J, Graham KS, Simonds AK, Morrell MJ (2010) Obstructive sleep apnoea syndrome is associated with deficits in verbal but not visual memory. Am J Respir Crit Care Med 182:98–103
9. Verstraeten E, Cluydts R, Pevernagie D, Hoffmann G (2004) Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. Sleep 27:685–693
10. Lis S, Krieger S, Hennig D, Roder C, Kirsch P, Seeger W, Gallhofer B, Schulz R (2008) Executive functions and cognitive subprocesses in patients with obstructive sleep apnoea. J Sleep Res 17:271–280
11. Saunamaki T, Himanen SL, Polo O, Jehkonen M (2009) Executive dysfunction in patients with obstructive sleep apnea syndrome. Eur Neurol 62:237–242
12. Berry DT, Phillips BA, Cook YR, Schmitt FA, Gilmore RL, Patel R, Keener TM, Tyre E (1987) Sleep-disordered breathing in healthy aged persons: possible daytime sequelae. J Gerontol 42:620–626
13. Telakivi T, Kajaste S, Partinen M, Koskenvuo M, Salmi T, Kaprio J (1988) Cognitive function in middle-aged snorers and controls: role of excessive daytime somnolence and sleep-related hypoxic events. Sleep 11:454–462
14. Hayward L, Mant A, Eyland A, Hewitt H, Purcell C, Turner J, Goode E, Le CA, Pond D, Saunders N (1992) Sleep disordered breathing and cognitive function in a retirement village population. Age Ageing 21:121–128
15. Kim HC, Young T, Matthews CG, Weber SM, Woodward AR, Palta M (1997) Sleep-disordered breathing and neuropsychological deficits. A population-based study. Am J Respir Crit Care Med 156:1813–1819
16. Boland LL, Shahar E, Iber C, Knopman DS, Kuo TF, Nieto FJ (2002) Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the Sleep Heart Health Study. J Sleep Res 11:265–272
17. Quan SF, Wright R, Baldwin CM, Kaemingk KL, Goodwin JL, Kuo TF, Kaszniak A, Boland LL, Caccappolo E, Bootzin RR (2006) Obstructive sleep apnea-hypopnea and neurocognitive functioning in the Sleep Heart Health Study. Sleep Med 7:498–507

18. Sforza E, Roche F, Thomas-Anterion C, Kerleroux J, Beauchet O, Celle S, Maudoux D, Pichot V, Laurent B, Barthelemy JC (2010) Cognitive function and sleep related breathing disorders in a healthy elderly population: the SYNAPSE study. Sleep 33:515–521
19. Redline S, Strauss ME, Adams N, Winters M, Roebuck T, Spry K, Rosenberg C, Adams K (1997) Neuropsychological function in mild sleep-disordered breathing. Sleep 20:160–167
20. Adams N, Strauss M, Schluchter M, Redline S (2001) Relation of measures of sleep-disordered breathing to neuropsychological functioning. Am J Respir Crit Care Med 163:1626–1631
21. Morgan BJ, Reichmuth KJ, Peppard PE, Finn L, Barczi SR, Young T, Nieto FJ (2010) Effects of sleep disordered breathing on cerebrovascular regulation: a population-based study. Am J Respir Crit Care Med 182:1445–1452
22. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP (1999) Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 131:485–491
23. Hiestand DM, Britz P, Goldman M, Phillips B (2006) Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. Chest 130:780–786
24. Kapsimalis F, Kryger M (2009) Sleep breathing disorders in the U.S. female population. J Womens Health 18:1211–1219
25. Hrubos-Strom H, Randby A, Namtvedt SK, Kristiansen HA, Einvik G, Benth J, Somers VK, Nordhus IH, Russell MB, Dammen T, Omland T, Kvaerner KJ (2010) A Norwegian population-based study on the risk and prevalence of obstructive sleep apnea. J Sleep Res [Epub ahead of print]
26. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM (2008) Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. Anesthesiology 108:822–830
27. Schmidt M (1996) Rey auditory and verbal learning test. A handbook. Western Psychological Services, Los Angeles
28. Egeland J, Rund BR, Sundet K, Landro NI, Asbjornsen A, Lund A, Roness A, Stordal KI, Hugdahl K (2003) Attention profile in schizophrenia compared with depression: differential effects of processing speed, selective attention and vigilance. Acta Psychiatr Scand 108:276–284
29. Rechtshaffen A, Kales A (1968) A manual of standardized terminology and scoring system for sleep stages of human sleep. University of California at Los Angeles, Brain Information Service/Brain Research Institute, Los Angeles
30. American Sleep Disorders Association (1992) EEG arousal: scoring rules and examples. Sleep 15:174–184
31. First Michael B, Spitzer Robert L, Gibbon Miriam, Williams Janet BW (1995) Structured Clinical Interview for DSM-IV Axis I Disorders, patient edition (SCID-I/P), version 2.0, Norwegian version
32. Beiske KK, Kjelsberg FN, Ruud EA, Stavem K (2009) Reliability and validity of a Norwegian version of the Epworth sleepiness scale. Sleep Breath 13:65–72
33. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14:540–545
34. American Academy of Sleep Medicine (2005) International classification of sleep disorders: diagnostic and coding manual. American Academy of Sleep Medicine, Westchester
35. Mitrushina M, Boone KB, Razani J, D'elia LF (2005) Handbook for normative data for neuropsychological assessment. Oxford Press, New York
36. Rund BR, Sundet K, Asbjornsen A, Egeland J, Landro NI, Lund A, Roness A, Stordal KI, Hugdahl K (2006) Neuropsychological test profiles in schizophrenia and non-psychotic depression. Acta Psychiatr Scand 113:350–359
37. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56:303–308
38. Gosselin N, Mathieu A, Mazza S, Petit D, Malo J, Montplaisir J (2006) Attentional deficits in patients with obstructive sleep apnea syndrome: an event-related potential study. Clin Neurophysiol 117:2235
39. Alchanatis M, Zias N, Deligiorgis N, Amfilochiou A, Dionellis G, Orphanidou D (2005) Sleep apnea-related cognitive deficits and intelligence: an implication of cognitive reserve theory. J Sleep Res 14:69–75
40. Mathieu A, Mazza S, Decary A, Massicotte-Marquez J, Petit D, Gosselin N, Malo J, Montplaisir J (2008) Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients. Sleep Med 9:112–120
41. Alchanatis M, Zias N, Deligiorgis N, Liappas I, Chroneou A, Soldatos C, Roussos C (2008) Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. Sleep Breath 12:17–24
42. Stickgold R (2005) Sleep-dependent memory consolidation. Nature 437:1272–1278
43. Zimmerman ME, Aloia MS (2006) A review of neuroimaging in obstructive sleep apnea. J Clin Sleep Med 2:461–471
44. Ayalon L, Peterson S (2007) Functional central nervous system imaging in the investigation of obstructive sleep apnea. Curr Opin Pulm Med 13:479–483
45. Yaouhi K, Bertran F, Clochon P, Mezenge F, Denise P, Foret J, Eustache F, Desgranges B (2009) A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res 18:36–48
46. Brzecka A (2005) Brain preconditioning and obstructive sleep apnea syndrome. Acta Neurobiol Exp 65:220
47. Veasey S (2009) Insight from animal models into the cognitive consequences of adult sleep-disordered breathing. ILAR J 50:307–311
48. Stepnowsky CJ Jr, Orr WC, Davidson TM (2004) Nightly variability of sleep-disordered breathing measured over 3 nights. Otolaryngol Head Neck Surg 131:837–843
49. Haensel A, Bardwell WA, Mills PJ, Loredo JS, Ancoli-Israel S, Morgan EE, Heaton RK, Dimsdale JE (2009) Relationship between inflammation and cognitive function in obstructive sleep apnea. Sleep Breath 13:35–41

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