Sleep disorders, sleepiness and the risk of traffic accidents

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Doctoral thesis

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Aidla Trading Kompendiet AB

This thesis is dedicated to my parents and my love Yashar

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ABSTRACT

The aim of this thesis was to identify the prevalence of sleep disorders, mainly obstructive sleep apnea (OSA), among public transport operators (PTO´s). Further to assess the risk of motor vehicle accident (MVA) in a group of patients with suspected OSA compared with the general population. Additionally, we aimed to identify specific risk factors linked to a history of MVA in these patients and to assess the prevalence of such factors in a large European sleep apnea patient database. We also determined the interventional effect of continuous positive airway pressure (CPAP) treatment on hypersomnolence, neurocognitive function and history of traffic accident. Finally, we investigated functional cognitive markers associated with history of MVA among PTO´s as well as single and multi-center cohorts of patients with OSA. The study used objective and subjective methods to assess sleep, sleep disorders, hypersomnia, vigilance and daytime cognitive performance. Data was extracted from a nationwide traffic accident registry (STRADA) for individual identification of MVA history. Sleep disorders including OSA, excessive daytime sleepiness, insomnia and restless legs syndrome (25%, 13%, 10% and 2%, respectively) were prevalent among PTO´s (n=87). Among clinical patients (n=1478) with suspected OSA the estimated risk of MVA was 2.5 times higher than in the matched general population. Measures of hypersomnolence, use of hypnotics, short sleep time, and driving distance (OR 2.0 to 2.7, $p \leq 0.02$) were associated with MVA risk, whereas conventional metrics of OSA severity were not. Compared with the general population, OSA patients were 1.9 times more likely to be injured in the MVA ($p=0.01$). We identified functional measures of neurocognitive dysfunction associated with MVA history ($p<0.01$). A mean nightly CPAP use of at least 4.0 hours was associated with improved neurocognitive function, reduced hypersomnia and a 70% reduction of MVA. It is concluded that conventional metrics of OSA are insufficient for the recognition of risk while markers of neurocognitive function may provide better identification of patients at risk. Our findings suggest that the high risk of MVA in OSA and the effectiveness of treatment in terms of accident reduction call for effective programs for detection and treatment of OSA.

Keywords: motor vehicle accident, obstructive sleep apnea, neurocognitive function
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1 SAMMANFATTNING PÅ SVENSKA

Obstruktiv sömnapné (OSA) förekommer bland 9 respektive 24% av kvinnor och män. Uttalad dagtidströtthet, försämrad kognitiv funktion och ökad risk för trafikolyckor (TO) har associerats med OSA. Denna avhandling avsåg att fastställa prevalensen av sömnstörningar och framförallt OSA bland yrkesförare samt att identifiera risk faktorer för TO risk bland så väl kliniska patienter som yrkesförare. Effekten nattlig övertrycksbehandling med mask (CPAP) utvärderades hos patienter avseende risk för TO och i ett vidare perspektiv utvärderades kognitiv funktion hos yrkesförare med nyupptäckt OSA före och efter CPAP behandling. Såväl subjektiva som objektiva testmetoder användes för att fastställa sömn, sömnstörningar, hypersomni och kognitiv funktion under dagtid. Vi analyserade registerdata avseende trafikolycksfall för att fånga 10-års incidens av TO bland patienter och kontroller. Sömnrelaterade störningar i form av OSA, uttalad dagtidssömnighet, insomni eller rastlösa ben (25%, 13%, 10%, respektive 2%) identifierades bland yrkesförare (n=87). Kliniska patienter (n=1478) med misstänkt OSA hade en 2.5 gånger förhöjd risk för TO jämfört med befolkningen i övrigt ($p<0.001$). Hypersomnolens, kort habituell sovtid, användning av sömnmedel och hög trafikexposition (OR 2.0 till 2.7, $p\leq0.02$) kunde associeras med ökad risk för TO. Däremot visade konventionella mått på svårighetsgrad av sömnapné ingen association med en ökad risk. Personskador relaterade till olyckan var 1.9 gånger vanligare bland OSA patienter jämfört med befolkningen ($p=0.01$). Vi identifierade fyra separata mått på kognitiv funktion i ett nykonstruerat dagtidstest som associerade med förekomst av TO ($p<0.01$). Behandling av OSA med CPAP var associerad med en kraftig reduktion av TO frekvens (från 7.6 till 2.5 TO/1000 förare och år). Denna reduktion visades enbart hos patienter som var följsamma med behandlingen (≥4 timmar/natt). Sammanfattningsvis talar objektiva och standardiserade nationella registerdata kring TO i en stor och väl karaktäriserad patientkohort för en påtaglig ökning av olycksrisk bland patienter med OSA. Prediktorer för risk kunde identifieras men konventionellt använda mått för att beskriva svårighetsgrad av OSA (t.ex. apné/hypopné index) bidrog inte till förbättrad identifikation av riskindivider. Våra data understryker betydelsen av att diagnostisera och behandla OSA i syfte att reducera TO frekvens. Avhandlingen illustrerar samtidigt utmaningen i att designa bättre verktyg för att identifiera patienter med OSA och ökad olycksfallsrisk i trafiken.

2 LIST OF ORIGINAL PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Karimi M, Eder DN, Eskandari D, Zou D, Hedner J, Grote L.

Impaired vigilance and increased accident rate in public transport operators is associated with sleep disorders
Accident Analysis and Prevention 2013; 51: 208-214

II. Karimi M, Hedner J, Häbel H, Nerman O, Grote L.

A sleep apnea related risk of vehicle accidents is reduced by CPAP - Swedish Traffic Accident Registry data
Submitted.

III. Karimi M, Hedner J, Lombardi C, McNicholas WT, Penzel T, Riha RL, Rodenstein D, Grote L.

Driving habits and risk factors for traffic accidents among sleep apnea patients – a European multi-center cohort study
Submitted.

IV. Karimi M, Hedner J, Zou D, Eskandari D, Lundqvist A-C, Grote L.

Vigilance and attention deficits are associated with motor vehicle accidents in sleep apnea patients
Manuscript.

3 CONTENT

4 ABBREVIATIONS

AASM	American academy of sleep medicine
ATP	Adenosine triphosphate
AHI	Apnea hypopnea index
ANT	Attention network test
BMI	Body mass index
BP	Blood pressure
CMD	Commercial vehicle drivers
CPAP	Continuous positive airway pressure
CTT	Continuous tracking test
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ESADA	European sleep apnea database
ESS	Epworth sleepiness scale
GABA	Gamma (ɣ)-aminobutyric acid
GOSLING	Gothenburg-oxford sleep resistance test
LC	Locus coeruleus
MVA	Motor vehicle accident
NREM	Non-rapid eye movement
OA	Oral appliance

ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PG	Polygraphy
PSG	Polysomnography
PTO	Public transport operators
REM	Rapid eye movement
SDB	Sleep disordered breathing
STRADA	Swedish traffic accidents data acquisition
SCN	Suprachiasmatic nucleus
TMN	Tuberomamillary nucleus
UPPP	Uvulopalatopharyngoplasty
VLPO	Ventrolateral preoptic nucleus
WHO	World health organization

5 INTRODUCTION

In January 29, 1886, Karl Benz designed the world's first modern three-wheeled automobile [1]. Six years later, in 1891, John William Lambert, an automotive pioneer hit a tree root when driving one of his own inventions and lost control over the car causing the first gasoline–powered automobile accident[2]. In 1953, Eugene Aserinsky, a pioneer in sleep research, discovered rapid eye movement (REM) sleep[3] and in 1998 Aserinsky fell asleep behind the wheel – which caused his death. Sleepiness at the wheel has been acknowledged as one of the major causes of fatality and traffic accidents[4]. In 2002, 37% of drivers in motor vehicle accidents reported they had fallen asleep behind the wheel[5].

5.1 Traffic safety

According to the world health organization (WHO) road traffic accidents are the leading cause of death among young people between the ages 15 and 29, and the eighth overall leading cause of death globally [6]. Automobiles have been steadily developed and become faster, safer and more "intelligent". Higher speed and the increased number of road traffic users have prompted for measures to increase traffic safety. In 2010, nearly 1.2 million people were killed on the roads around the world and more than 50 million persons suffered from non-fatal injuries [6, 7], some of them disabled for life. The global economic cost of road crashes has been estimated to 518 billion US$ [7], not to mention the economic burden and suffering of individuals and their families. Improvement of traffic safety has therefore been prioritized in almost all societies around the world. Indeed, efforts including rumble strips, 2+1 lanes, roadside protection, improved road light, speed limits and traffic regulations, driving legislations on medication and alcohol consumption, air bags, safety belts, and child safety seats have led to substantial improvements of safety. In fact the European Union (EU) recently published data on the successful reduction of motor vehicle accidents (MVA) in the member states by 43% between 2001 and 2010 [4]. However, despite the precautions and legislation passed to improve traffic safety MVA´s are still frequent. By 2020, if appropriate countermeasures are not taken, it is estimated that road traffic accident may have increased by 80% in low- and middle income countries[8, 9]. The Swedish government approved of the "Vision Zero" road safety program in 1997, with the goal to have zero road traffic fatalities or injuries. Indeed, in 2012 the number of road traffic fatalities had been reduced by 50% from 541 to 285[10, 11]. Swedish roads have now become among the safest in the world and several countries are following the initiative of "Vision Zero". By 2020, the EU aims at

having reduced road casualties by 50% as part of the European Road Assessment Program [12]. The technical aspects of traffic safety have and will continue to progress and systematic analyses of human factors related to traffic safety now constitute focus areas in research and governmental activities.

5.2 Human factors involved in traffic accident risk

Exposure to traffic

Annual driving distance as a measure of exposure to traffic is associated with the risk for MVA. As expected, time spent behind the wheel has been found to be associated with increased risk of sleep-related crashes and drowsy driving[13] among commercial[14] as well as private drivers[15]. In fact, 50% of European drivers spend between 5,000 and 15,000 km per year on the road and approximately 6% drive more than 30,000 km annually [16]. Comparing men and women, 65 and 39% respectively, drive more than 10,000 km per year[16]. Restricted sleep may compromise an individual´s capability to maintain alertness over longer periods of time. The combination of sleepiness and driving has been identified as an important risk factor for MVA and the excess risk of accidents attributable to sleepiness has been estimated to 10 – 20%[15, 17-20,21]. Several countries have legislated around the maximum number of hours per 24 h that could be spent behind the wheel. However, these are mainly regulations which apply to commercial rather than private drivers[22].

Gender, age and circadian influence

Established risk factors associated with an increased risk of MVA include young age and male gender [23] (figure 1). Younger drivers (<25 years of age) are in general less experienced, less capable of predicting potentially "dangerous" situations in their traffic environment, and tend to more often drive during nighttime [18]. Despite a strong functional pressure to sleep, adolescents and younger individuals tend to stay up later at night and more frequently drive during hours associated with increased traffic accident risk [18, 24]. This is particularly evident in countries where the minimum legal age of license holding is 16 years. Younger male drivers tend to have more accidents during vulnerable hours of the day between 02.00 to 07.00 when compared with drivers aged 30 years and above[17] (figure 2). This risk behavior has not been reported in younger females.

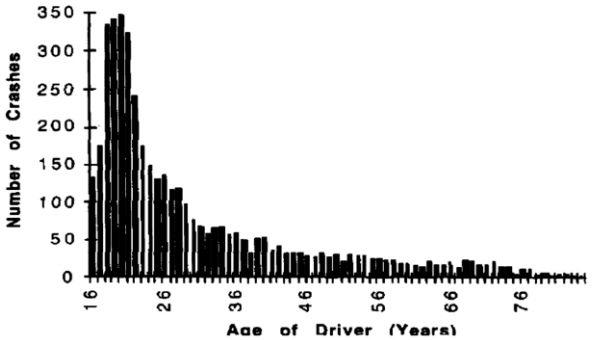


Figure 1. Frequency histogram of number of crashes at different ages (X axis) in which the driver was not intoxicated but judged to have been asleep. Reprinted from Pack et al. Accid. Anal. and Prev. 1995; 769-775,[18] with permission from Elsevier.

Another important circadian window for increased incidence of MVA´s occurs between 13.00 and 15.00, in the so called mid-afternoon "siesta" hours (figure 2). Conversely, the incidence of accidents has been found to be lower during hours of the day associated with a high degree of alertness (e.g. 09.00 and 11.00 am, and 19.00 and 21.00)[17, 18, 25-27]. This temporal association between circadian propensity to sleep and overrepresentation of accidents suggests a possible causal relationship. Indeed, individuals with work schedules during circadian hours associated with increased sleepiness such as nighttime or shift work have an increased risk of sleepiness related MVA[22, 28]. Despite the methodological difficulties to identify accidents primarily caused by sleepiness at the wheel there is certainly emerging evidence pointing to the importance of managing sleepiness at the wheel[13, 29].

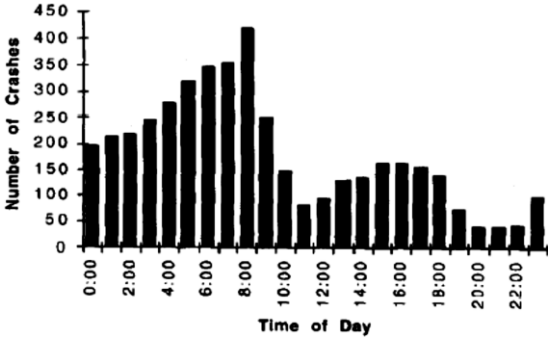


Figure 2. Frequency histogram of time of occurrence during the day of crashes in which the driver was judged to be asleep but not intoxicated. Reprinted from Pack et al. Accid. Anal. and Prev. 1995; 769-775[18] with permission from Elsevier.

5.3 Sleep

The function and regulation of sleep

- Why do we sleep?

During the past centuries our knowledge about the physiology, pathology and the regulation of sleep has advanced considerably and we have come closer to the understanding of why we sleep. The sleeping infant is a good example of the crucial role sleep plays in brain development and learning capacity of children. Infants spend more than half their day asleep and a large proportion of this time is spent in rapid eye movement (REM) sleep. Brain plasticity is largely stimulated during sleep which is believed to play a major role in the development of the central nervous system[30]. The restorative[31] and modulating effects of sleep are also important for muscle growth, immune defense function, growth hormone secretion [32], glucose metabolism, and cardiovascular control[33].

In order to understand the function of sleep, a frequently used approach is to study the consequences of restricted or fragmented sleep. For example, partial or complete sleep restriction has been found to induce dysfunction in memory and interfere with memory consolidation and learning capacity[34, 35]. Attention deficits and impaired cognitive daytime performance are also consequences of poor sleep quality and sleep restriction[36]. Sleep deprivation has been identified as an epidemic condition in industrialized nations and as an increased risk factor of motor vehicle accident[37].

"…indeed, our entire life takes place in the alternating change of two biological conditions, the waking and the sleeping state" Von Economo, C., 1926.

The sleep and wakefulness regulating regions of the brain were specifically described by the neurologist Von Economo in his work on encephalitis lethargica in 1916[38-40]. Maintenance of sleep and wakefulness includes several cell groups located in the brainstem, hypothalamus and basal forebrain – the ascending arousal system – projecting to the cerebral cortex. Wakefulness is promoted, but not limited to release of a complex neuronal system including noradrenergic activity in the locus coerules (LC), histamine neurons in the tuberomamillary nucleus (TMN) and orexin (hypocretin) in the posterior hypothalamus[39].

Sleep on the other hand, is mainly promoted by hypothalamic activity in the ventrolateral preoptic nucleus (VLPO), which is rich in the neurotransmitters ɣ-

aminobutyric acid (GABA) and galanin. These neurons promote sleep in part by inhibiting the monoaminergic- and cholinergic neurons in the pontine region. Acetylcholine secretory neurons in the upper pons are particularly active during rapid eye movement (REM) sleep. The transition between wakefulness and sleep appears to involve a sharp modulatory function which has led to the postulation of the so called flip-flop switch. This switch is actively stabilized by the orexin neurons in the hypothalamic region[39, 40].

The regulation of sleep includes the ***two process model*** – process S and process C. The ***homeostatic regulation*** of sleep, also known as the sleep-wake dependent ***process S***[41, 42], is proposed to be regulated by accumulating levels of adenosine. During prolonged wakefulness and energy consumption, adenosine triphosphate (ATP) is degraded and extracellular adenosine levels rise in the basal forebrain. This promotes GABAergic neuron activity and non-REM (NREM) sleep is initiated[43-45]. The *circadian regulation* of sleep, known as ***process C***, includes the 24-hour circadian rhythm regulated by activity in the suprachiasmatic nucleus (SCN). The SCN located in the hypothalamus rostral to the optic chiasm, provides the anatomical and functional construct of the biological clock [46]. External triggers including light appear to modulate the activity of the circadian regulation. The SCN is synchronized in the photoreceptive retinal ganglion, which contains receptors for melatonin and the photopigment melanopsin and cryptochrome [47]. The efferent projections from the SCN to the VLPO, lateral hypothalamus and locus coeruleus (LC) are important for the sleep-wake cycle. The inhibition of VLPO is blocked when the SCN signal is decreased and NREM sleep is initiated[39, 40].

The homeostatic as well as the circadian regulation of sleep are important for daily functioning and safety, especially for the risk of MVA´s. Acute disruption of the circadian regulation of sleep can be altered acutely by jet lag or chronically following shift-work [27, 48]. Poor or disrupted sleep due to sleep disorders such as sleep apnea may lead to impaired homeostatic sleep drive and need for restorative sleep. Consequently, the risk for decrements in judgment, performance and alertness due to excessive sleepiness is increased [27].

The physiology of sleep

Sleep is divided into two major stages known as REM[3] and non-REM (NREM) sleep [49]. NREM is further divided into stages N1 – N3 and is more pronounced during the early part of the night. The likelihood of REM sleep occurrence increases further into the night and is most apparent closer to early morning hours. Sleep usually proceeds in 90 minute cycles of the order N1 – N2 – N3 – N2 – REM [50, 51]. The various stages of sleep are visualized using a nocturnal polysomnographic (PSG) recording, a

technique which includes electroencephalographic (EEG), electromyographic (EMG), and electrooculographic (EOG) activity[52, 53].

Stage N1 sleep is defined as the phase between wakefulness and sleep, the time before nodding off. It is characterized by slow rolling eye and blink movements. The muscles are somewhat active and transition from alpha waves (frequency 8–12 Hz), seen during wakefulness, to theta waves (4–7 Hz) is prevalent in the EEG. As sleep progresses into ***stage N2*** typical graphic elements like high voltage and low frequency (11–16 Hz) activity of sleep spindles and isolated high voltage K-complexes appear in the surface EEG. The arousal threshold is clearly elevated. Less EMG activity and reduced heart rate are also characteristic for this stage. Adults spend 45–55% of their total sleep time in N2. ***Stage N3***, called *slow-wave sleep (SWS)*, consists of at least 20% delta waves (0.5–2 Hz) with a peak-to-peak amplitude greater than 75μV. SWS is known as "deep sleep", reflecting the further elevation of the arousal threshold and dream activity is rather monotonous during SWS. Most sounds from the surroundings are now less likely to disrupt sleep and this stage accounts for approximately 25% of the total sleep time. However, SWS is important for a number of bodily functions including the integration of memories[54] and the stimulation of growth hormone secretion[55].

REM sleep, accounts for 20-25% of sleep time and is characterized by slow rolling eye movements in the EOG and muscle atonia seen in the EMG. It is also known as paradoxical sleep because of the presence of higher frequency saw-tooth EEG patterns similar to alpha and beta (8–13 Hz) waves during the wake state. REM sleep is associated with substantial cortical activity reflected by vivid dreaming. Another important feature of REM sleep is a relaxation of all voluntary musculature resulting in REM-atonia. This may be interpreted as a protective means against the vivid dreaming. REM sleep is characterized by an increased arousal threshold. Heart rate variability is increased[33] and respiration becomes irregular[56]. This stage has also been found to play a major role in the consolidation of memories[57].

Microsleep

Microsleep is characterized by short episodes of light sleep; stage N1, in periods of wakefulness. It can behavioral and characterized as closed or rolling eyes and short periods of muscle atonia and inattention. Alternatively, microsleep can be detected by EEG methods and is characterized by theta waves (Stage N1)[58]. Microsleep may occur in any individual during monotonous situations and is provoked by sleep restriction. Driving simulator studies have shown that impairments in performance and vehicle control in patients with OSA[59] and healthy individuals[60] is associated with microsleep.

Sleep disorders

Beside the social and behavioral aspects that may influence traffic safety, sleep pathology is of importance when it comes to deterioration of "normal" daytime functioning. Several sleep disorders lead to non-restorative sleep which may cause excessive daytime sleepiness, fatigue, attention and memory deficits, irritability and impaired performance. Sleep disorders can be subclassified into sleep related breathing disorders, hypersomnia, insomnia, circadian rhythm disorders, parasomnia, and sleep related movement disorders (ICSD-2) [58].

Circadian rhythm disorders include several conditions associated with disrupted circadian control of sleep and wakefulness. For instance, delayed or advanced sleep phase disorder, as well as shift work and jet lag involve poor alignment with the circadian system. Some of the circadian rhythm disorders appear to result from a dysfunctional SCN but can often be a consequence of life-style and contain a social component[58].

Parasomnias are subdivided into disorders with arousal from NREM sleep and from REM sleep[61]. The group of NREM arousal disorders includes sleep-walking, nightmares, sleep paralyses, and sleep-related eating disorders [58]. Patients may suffer from sleep apnea as a trigger for the dysfunctional arousal from sleep.

Sleep related movement disorders include the periodic limb movement disorder (PLMD) characterized by involuntary movement of the limbs mainly during NREM sleep and typically associated with arousals. PLMD is prevalent and affects approximately 34% of adults. Restless legs syndrome (RLS) is a neurologic disorder characterized by dysesthesia, particularly in the legs, that occurs during resting conditions while awake as well as during sleep. This frequent disorder may require specific treatment particularly when sleep is affected[58].

Insomnia is described as a difficulty to initiate and/or to maintain sleep, with early awakenings and complaints of non-restorative sleep. Chronic insomnia is prevalent in 12 and 20% of the general population and can occur with or without comorbidities like psychiatric disease, chronic pain, RLS or severe cardiac and pulmonary disease. Chronic insomnia is associated with daytime fatigue and impaired daytime function but rarely sleepiness. Female gender, age >60 years, stress, shift-work, jet lag as well as several medical disorders have been associated with an increased risk of insomnia[58, 62]. Vice versa, insomnia increases the risk for psychiatric disease.

Hypersomnia is defined as the incapability to maintain adequate wakefulness during daytime. Narcolepsy with or without cataplexy and, idiopathic and recurrent hypersomnia are classified as hypersomnias of central origin[58]. Other underlying

sleep disorders such as sleep apnea or PLMD may also result in daytime hypersomnia. Psychiatric disease has also been found to be associated with significant hypersomnia[63].

Sleep related breathing disorder (SRBD) describes a number of conditions characterized by a destabilization of breathing during sleep. The episodes with disturbed breathing are clinically divided in obstructive and central[64] sleep disordered breathing events. A specific group of SRBDs is characterized by severe nocturnal hypoxia and is referred to as sleep related hypoventilation syndromes. SRBD are frequently observed and often, but not always, linked to CV and/or metabolic diseases. SRBDs may cause severe hypersomnia[58].

It is proposed that sleep disorders associated with an increased MVA risk are mainly those with symptoms of excessive daytime sleepiness. Patients diagnosed with sleep apnea and narcolepsy account for approximately 70% of all sleep-related accidents [65]. However, there are inconsistencies in data reporting on MVA risk among patient diagnosed with insomnia. This variability might due to the variety of underlying conditions associated with insomnia or the fact that neurocognitive deficits are less frequently observed in insomniacs when compared with normal sleepers.

5.4 Obstructive sleep apnea

Pathophysiology and diagnostics

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of total or partial (apneas or hypopneas) occlusion of the upper airway. The airflow reduction is usually associated with a reduction in blood oxygen saturation (hypoxia). The duration of apneas and hypopneas is by definition at least 10 seconds and frequently more pronounced during REM sleep because of the progressive muscle relaxation observed in this sleep stage. The upper airway obstruction leads to variable degree of hypoxia and is terminated by a CNS arousal. Repetitive breathing events result in sleep fragmentation and may severely alter the physiological sleep structure[66-68]. Figure 3 illustrates the occurrence of more than 4 sleep cycles (upper panel) – stages NREM (N1, N2, N3) and REM (R) in a patient with OSA. However, these cycles are frequently interrupted by wakefulness (W). Even longer periods of wakefulness occur during the night (around 03.00). Overnight oximetry (SaO_2%) shows frequent minor desaturations as a sign of sleep apnea, here mainly hypopnea. Sleep fragmentation is accompanied by autonomic activation visible in heart rate accelerations (figure 3).

OSA is diagnosed by either overnight PSG or polygraphy (PG). Respiratory events are recorded by means of nasal cannula, respiratory effort belts together with finger pulse oximetry[69]. Mild, moderate and severe degrees of OSA are defined by an apnea-hypopnea index (AHI) of 5-<15, 15-<30 and ≥ 30 events per hour (n/h) of sleep, respectively.

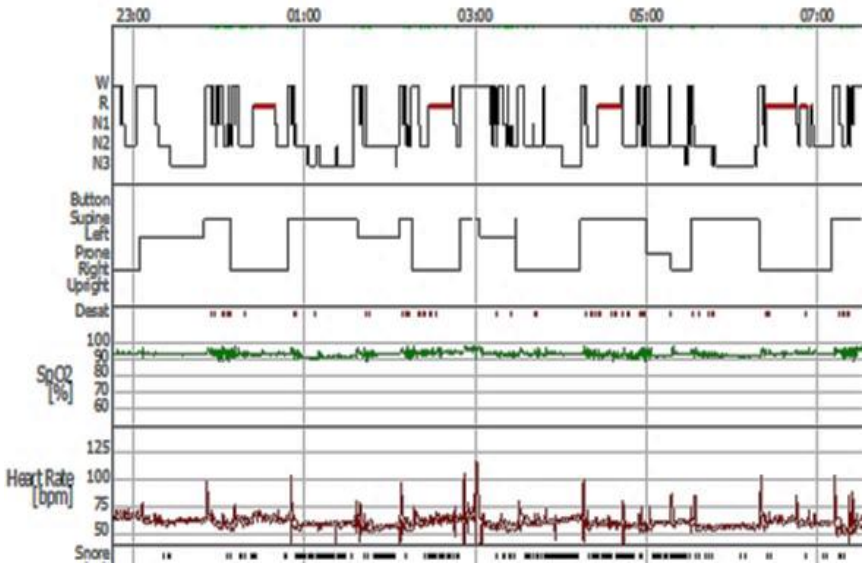


Figure 3. The hypnogram illustrates the occurrence of four sleep cycles in a patient with OSA. The sleep continuum is altered by frequent arousals and even longer periods of wakefulness. Slep apnea leads to repetivie episodes of hypoxia seen in the oximetry channel (SaO2). Abbreviations: W=Wake, R=REM, N1=NREM stage 1, N2=NREM stage 2, N3=NREM stage 3, SaO_2=Oxygen Saturation.

Epidemiology

The prevalence of sleep apnea, defined by an AHI ≥5 n/h, in the general population has been found to be 9 and 24% among middle-aged women and men, respectively[66]. The prevalence of symptomatic sleep apnea among men and women is approximately 4 and 2%, respectively[66,70]. These high prevalence numbers have been even extended further in recent epidemiological studies[71, 72].

Risk factors

Risk factors associated with OSA include male gender[73], menopause[74], central and abdominal obesity, craniofacial and upper airway abnormalities[75, 76], and alcohol consumption before bedtime[70] (table 1). Data from the Wisconsin Sleep Cohort Study suggested that a 10% increase in body weight was associated with a 6-fold risk of developing moderate to severe OSA[77].

Consequences of OSA and comorbidities

Sequelea associated with OSA are excessive daytime sleepiness, irritability as well as impaired memory and attention. Comorbid systemic hypertension, cardiovascular disease[78], diabetes mellitus and metabolic disorder[79, 80] are overrepresented in patients with OSA[81] (table 1).

Treatment of OSA

Continuous positive airway pressure (CPAP) was first introduced by Sullivan in 1981[82] and is the most efficient treatment of OSA[83]. The positive airway pressure applied via a nasal mask prevents upper airway collapse, leading to elimination of apneas and hypopneas followed by improved blood saturation levels and restoration of sleep. Other treatment options are oral appliances (OA) mainly in patients with mild to moderate sleep apnea[83] and surgical interventions like tonsillectomy or uvulopalatopharyngoplasty (UPPP) in specifically selected cases[84] (table 1).

Behavioral treatment options for patients with mild OSA include active weight reduction and positional therapy by avoiding the supine position [85]. Consumption of alcohol [86] and sedatives should also be avoided [72]. Recent therapeutic developments include hypoglossal nerve stimulation which resulted in an approximately 70% reduction of AHI in carefully preselected OSA patients [87] (table 1).

Table 1. Obstructive sleep apnea - risk factors, symptoms, comorbidities and treatment.

Risk factors	**Symptoms**	**Comorbidities and Consequences**	**Treatment**
Male gender Increasing age Obesity/overweight Menopause Smoking Craniofacial/upper airway abnormalities Alcohol consumption before bedtime	EDS Snoring Witnessed apnea Headache Irritability Nocturia Sweating Insomnia	Impaired cognitive function CVD e.g. hypertension Diabetes and metabolic disorder MVA risk	CPAP MAD Upper airway surgery Positional therapy Weight reduction

OSA and motor vehicle accidents

Previous studies have reported that individuals diagnosed with OSA have a 2 to 7 fold elevated risk of MVA[18, 88-91]. In 1988 Findley et al.,[91] investigated the association between OSA and MVA risk and found that patients diagnosed with OSA have a 2.6 times higher MVA rate when compared with individuals without OSA. Furthermore, an almost six fold higher odds ratio for a MVA leading to emergency care was reported in patients with mild to moderate OSA compared with an age and sex matched controls group selected from general practitioners[90]. Several additional investigations have addressed the association between OSA and risk of MVA [92-94] but MVA data were assessed from subjective reports [92, 95-97] which, due to uncertainty and recall bias, provide limited accuracy in terms of MVA prevalence. However, a recent meta-analysis suggested an OR of 2.5 for the association of between OSA and MVA risk [29]. A remaining limitation is that most studies fail to adjust for traffic exposure, defined as driving distance [65, 98], which represent an important confounder in studies of MVA risk.

Further evidence on a causal role of OSA in the elevation of MVA risk is provided by treatment studies. OSA treatment with CPAP has been linked to a reduction of MVA risk[89, 99, 100]. A recent meta-analysis including nine studies[89, 97, 101-107] conducted by Tregear et al. [108] demonstrated that CPAP treatment reduced MVA risk by 72% (risk ratio of 0.28, 95% CI 0.22-0.35). This study identified limitations in terms of study design, study power, incomplete CPAP compliance data and/or reported MVA data reliability in the reviewed studies. Seven[97, 101, 103-107] out of nine studies

evaluated subjectively reported accident frequency before and after CPAP whereas only two smaller studies in the US and Canada, by George et al., and Findley et al., [89, 102] used objective MVA data from the Ontario Ministry of Transportation (MTO) database and the Department of Motor Vehicles (DMV) of the State of Colorado.

The fragmented sleep caused by respiratory arousals and the reduction in blood oxygen levels resulting from apnea are both believed to contribute to the symptoms of excessive daytime sleepiness, which are common in OSA [109]. Despite the possibly beneficial effect of CPAP on MVA risk [89, 101] it remains unknown if OSA patients without EDS [110], the so called "asymptomatic OSA patients", carry an increased risk of MVA. Moreover, the amount of CPAP treatment needed to reduce risk is poorly known. It is known that up to 50% of all CPAP users have treatment compliance below the conventionally applied cut-off ≥4 hours/night[111]. AHI and ODI represent the most frequently used metrics of apnea severity. They are also markers used to determine therapeutic efficacy. However, data suggesting an actual dose response relationship between OSA severity and MVA risk are not consistent [112] and most studies have been unable to find such a relationship [14, 93, 103, 113]. Aldrich reported on a relationship between MVA and severe sleep apnea (RDI >60) and lower minimum SpO_2, but this was only significant among males [65]. Despite the strong association between OSA and MVA risk, the task to identify individual patients at risk based on apnea severity remains to be a challenge in clinical practice, especially since increased MVA frequency occurs only in a subgroup (5%) of OSA patients [114, 115].

5.5 Impaired vigilance at the wheel

The terms "sleepiness" along with fatigue [28] and drowsiness are widely used in studies of OSA and MVA risk and the definitions are debated [27]. Sleepiness is often described as the tendency to fall asleep and includes apparent symptoms of yawning, increased duration of eye-blinks and a reduced activity level [48]. Sleepiness is often caused by sleep deprivation, poor sleep quality or prolonged wake[116]. The term "drowsiness" has been used in parallel with "sleepiness" especially in drivers and includes the tendency to fall asleep [117]. On the other hand, the term "fatigue" includes not only sleepiness caused by time awake, but can also be task specific caused by time-on-task and cognitive work load [118 119 27]. Fatigue can be restored by sleep, but may also be managed by resting, by shifting the specific work task [116] or by shorter working hours[120]. Fatigued, sleepy and drowsy driving have been found to be associated with MVA risk[5, 121,4, 19].

5.6 Neurocognitive function

In general, cognitive function can be described as the ability to perform adequately in terms of memory and language skills, intelligence, psychomotor and executive function, speed of mental response, planning and decision making, as well as sustained attention during wakefulness. Several neural networks and neurotransmitters in various regions of the brain provide components that contribute to both simple and complex levels of neurocognitive function. Functional neuroimaging studies[122,123] indicate that regions in the frontal, parietal and the temporal lobe are particularly relevant in this context. In detail, cholinergic projections from the parietal junction and frontal eye field, adrenergic projections from the LC and the parietal cortex, as well as dopaminergic projections from the basal ganglia and anterior cingulate to the cortex have been described to be functionally linked to neurocognitive function[124].

Several disorders of the CNS have been identified to affect neurocognitive function. For instance, Alzheimer´s disease affects memory[125], whereas certain traumas or brain tumors may affect behavior and personality traits[126]. Studies on acute and chronic sleep restriction have shown that subjective alertness and attention is impaired. Further, polymorphisms in certain clock genes (PERIOD 3) appear to have a modulating effect on cognitive impairment[127]. Sleep restriction in healthy adults have specifically been shown to produce slower reaction times and cognitive performance deficits in the psychomotor vigilance test (PVT)[36] as well as impairment in memory functions[128]. The attention network test (ANT) was developed to examine three domains of attention; the orienting, alerting and executive function[129]. Sleep deprivation[130] has been associated with reduced vigilance and impaired orienting and executive function in the ANT. Moreover, fluctuations in visuo-spatial performance assessed by the compensatory tracking task (CTT), has been able to detect time-on-task effect and decrements in alertness[131].

Cognitive function and OSA

Several domains of cognition appear to be impaired in patients diagnosed with OSA[132-134]. The exact underlying mechanism(s) of these impairments are unknown but nocturnal hypoxemia has been associated with typical abnormalities of tasks involving the frontal lobe such as learning, planning, and short-term memory[135], [132]. Studies have reported [136, 137] on deficits in attention and executive function [138] as well as in psychomotor function in OSA patients although dimensions of intelligence and verbal ability have not been shown to be systematically affected. The effect of CPAP treatment on neurocognitive deficits in OSA appears to be particularly strong in terms of improved attention and alertness[133]. Ferini-Strambi et al.[139] found a partially reversible effect of cognitive dysfunction in terms of attention, visuospatial and

motor performance after 15 days of CPAP therapy Whereas, after 4 months of treamtent no further improvements were found[139]. However, Naegele et al.[140] found that 4 to 6 months of CPAP therapy improved cognitive domains involving executive function and learning, but not short-term memory. A review[141] of cognitive impairment in patients with sleep disorders proposed that patients diagnosed with moderate to severe sleep-related breathing disorder (SRBD) had a poorer performance in attention tasks in a driving simulator when compared with either insomniacs or with controls. A complete reversal of cognitive deficits following CPAP treatment might not be experienced in all patients with OSA[142].

Assessment of cognitive function in OSA

Objective methods

Common tests used to examine the potential influence of OSA on cognitive function primarily focused on sustained attention and performance during monotony. Excessive daytime sleepiness is objectively assessed by means of the ***Maintenance of Wakefulness Test (MWT)*** or the ***Multiple Sleep Latency Test (MSLT)***[143]. The MWT is used to determine the ability to stay awake during monotonous conditions such as sitting in a darkened room during four 40 min test sessions with breaks between each session. The MSLT is performed during a 20 min period 5 times with 2 hour breaks between each session and measures the ability to fall asleep lying in a darkened room. Sleep latency is determined as main outcome in both tests[144]. Both tests are prone to motivational bias and it may be argued that they do not reflect the actual ability to stay awake during prolonged daytime monotony [145], [146], such as during driving conditions. Moreover, both tests are time consuming and require sleep EEG montage to determine sleep latency. Their capacity to predict MVA risk in an OSA population has been debated [65, 88, 147] and has not been prospectively evaluated. The ***Oxford Sleep Resistance*** (OSLER) test was developed as a simple monotony test to assess sleep latency by measuring speed of response to stimuli and attention [148]. Other non-EEG based functional tests applied in the context of MVA risk prediction in OSA include driving simulators [93, 149], real time driving[150] and the ***Psychomotor Vigilance Test*** (PVT) [151] . The PVT is also a simple reaction time test which reflects and measures sustained attention. There is a lack of validation studies on these cognitive tests that includes objective assessment of MVA history.

Subjective methods

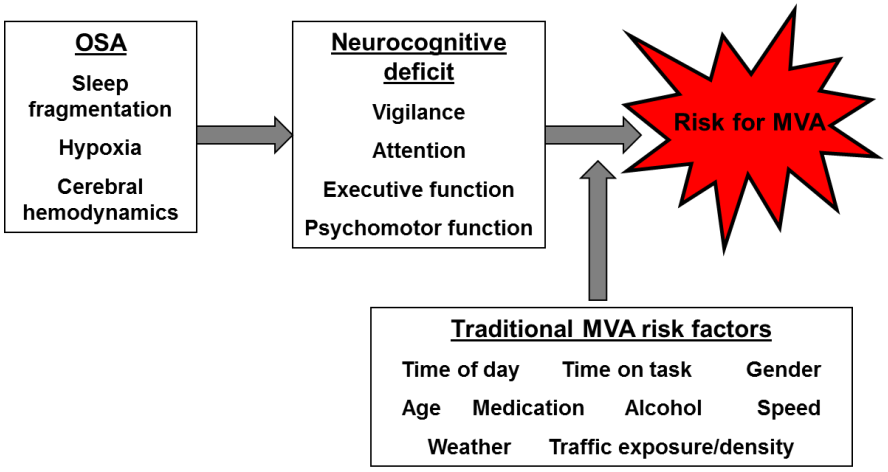
Several questionnaire based methods are used to assess daytime sleepiness. The ***Epworth Sleepiness Scale (ESS)*** [152] is one of the most widely used questionnaires to evaluate general level of daytime sleepiness. Other validated questionnaires are the ***Stanford Sleepiness Scale (SSS)*** [153] and the ***Karolinska Sleepiness Scale (KSS)*** [154] which both measure the prevailing state of sleepiness. Limitations of self-reported

sleepiness assessments include recall bias and the unwillingness of some individuals to realize the extent of their daytime sleepiness.

Cognitive function and prediction of MVA risk in OSA

Driving is a complex task that requires simultaneous processing of visual information, sustained attention, and psychomotor function. Clearly, these functions may be compromised due to excessive sleepiness. In fact, 20% of traffic fatalities are assumed to be caused by impaired vigilance at the wheel [21].OSA is characterized by sleep fragmentation, repetitive hypoxia and prolonged alteration in cerebral hemodynamics [155]. OSA severity in terms of apneic events failed to consistently predict MVA risk in a recent meta-analysis [29]. EDS, for instance operationalized by the Epworth Sleepiness Scale (ESS) score [152], provided only a weak predictor of risk[156]. The PVT did not predict risk of MVA and few tests have been validated against objective accident data and traditional MVA risk factors have not been carefully controlled for (figure 4). Hence, there is a lack of validated objective methods for prediction of MVA risk in OSA. In the current thesis we aimed to overcome at least in part the limitations of previous studies in the studies of MVA risk in OSA populations.

Figure 4. The possible relationships between the consequences of OSA, neurocognitive deficits, established risk factors and MVA risk.



6 AIM OF THIS THESIS

The overall aim of this thesis was to characterize the contribution of sleep disorders, in particular OSA, on the risk of MVA. In detail, we aimed to

1. Paper I
   investigate the prevalence of sleep disorders and the functional neurocognitive consequences of OSA in a group of public transport operators.

2. Paper II
   examine the actual accident rate in patients with suspected OSA and the effect of CPAP treatment. Furthermore, we aimed to identify clinical characteristics of patients with OSA and a history MVA of MVA.

3. Paper III
   describe the prevalence and regional distribution of previously identified (paper II) clinical characteristics associated with a MVA history in a large cohort of European patients with suspected OSA.

4. Paper IV
   identify functional measures of neurocognitive performance associated with a history of MVA in patients diagnosed with OSA.

7 METHODS

7.1 Study population and design

Ethical consideration

All studies were approved by the ethical review board at the University of Gothenburg and in paper III the board of each participating center. Written and signed informed consent was collected from all study participants.

Table 2. Details of the study populations investigated in papers I through IV.

Paper	Cohort	Design (n)	CPAP treatment Yes/No	MVA Objective/ subjective
I	PTO	Prevalence (n=101) Intervention (n=12)	Yes	Subj.
II	OSA patients	Retrospective (n=1718) Case-control (n=82 and n=21118)	Yes	Obj.
III	OSA patients	Cross-sectional (n=8476)	NA	NA
IV	OSA patients	Retrospective (n=114) Case-control (n=11 and n=103)	NA	Obj.

Abbreviations: PTO=Public Transport Operators, OSA=Obstructive Sleep Apnea, CPAP=Continuous Positive Airway Pressure, MVA=Motor Vehicle Accident, Subj.=Subjective, Obj.=Objective, NA=not applicable.

Paper I

Subjects were recruited among a group of bus or tram operators (PTO) at the Gothenburg public transport company (n=550). All individuals received oral and written information concerning the study and volunteered to participate (n=101). Information regarding study participation or findings in the study was not carried on to the employer. The prevalence of sleep disorders in this group of PTO´s (n=87) was investigated and daytime neurocognitive function was compared before and during intervention in subjects (n=12 out of 22) diagnosed with OSA (table 2).

Paper II and III

The European Sleep Apnea Database (ESADA) is a large ongoing prospective cohort study which started in 2007[157]. The database includes randomly selected patients with suspected OSA referred to 25 clinical sleep centers, 21 of them affiliated to universities, in 18 countries. The data reported in ***paper II*** and ***III*** include patients recruited between 2007 and 2012.

Paper II included patients with suspected OSA contributed by the Gothenburg site (n=1718) into the ESADA cohort. Subjects holding a driving license (DL) (n=1478) were identified in the *Swedish Traffic Accident Data Acquisition (STRADA)* [10] registry. MVA history was obtained for those patients who were drivers at the time of the accident. In order to compare the MVA risk between patients and the general population a balanced control group (n=21118) from the same residential area as the hospital capture area was obtained from the STRADA (table 2).

Paper III included a wider sample of patients (n=8476) from the different European ESADA centers. Risk factors identified in study II were further examined among patients (n=6984) holding a DL and regional differences were characterized in this group of European patients with suspected OSA (table 2).

Paper IV

Patients were recruited from three separate study cohorts comprising clinical OSA patients (sub-cohort I, n=58), OSA patients from a smaller randomized and controlled pharmacotherapy study (sub-cohort II, n=43)[158] and a sub-group of individuals (sub-cohort III, n=13) from paper I (table 3). The criteria for inclusion in the main cohort were based on availability of data from an identical neurocognitive test procedure, information on OSA severity, and anthropometry data. Retrospective MVA history was obtained by identifying patients (n=11) appearing in the STRADA registry (table 2).

Table 3. Characteristics of the three sub-cohorts included in the main cohort of paper IV (n=114).

	Sub-cohort I N=13	Sub-cohort II N=58	Sub-cohort III N=43	P-value
Male, n (%)	11 (84.6)	34 (58.6)	40 (93.0)	0.001
Age, years	53.0 [41.5-56.0]	52.5 [43.7–62.2]	53.0 [42.0–61.0]	0.8
BMI, kg/m^2	28.1 [26.3-33.2]	28.4 [25.3–33.4]	30.9 [29.3–32.9]	0.1
AHI, n/h	17.6 [11.6–34.9]	11.2 [2.1–34.1]	43.3 [25.6–61.5]	<0.001
ODI, n/h	12.9 [5.2–30.1]	7.5 [1.0–26.5]	34.6 [22.1–60.6]	<0.001
TST, min	449.2 [345.3–469.5]	363.0 [302.5–429.0]	411.7 [366.2–431.6]	0.01
ESS score	9.0 [4.5–12.5]	12.0 [7.4–16.2]	12.0 [9.0–17.0]	0.08
MVA, n (%)	1 (7.7)	8 (13.8)	2 (4.7)	0.2

Abbreviations: BMI=Body Mass Index, AHI=Apnea Hypopnea Index, ODI=Oxygen Desaturation Index, TST=Total Sleep Time, ESS=Epworth Sleepiness Scale, MVA=Motor Vehicle Accident. Statistics: Non-parametric Kruskal Wallis H test for between group differences and Games-Howell Post Hoc test for multiple comparisons of categorical variables (MVA and gender), p-value <0.05 was considered significant. Data are presented as median [interquartile range].

Anthropometry and clinical data

Anthropometric information assessed in all papers include age (years), gender (female/male), body mass index (BMI, kg/m^2), height and body weight (table 4).

A clinical history of comorbidities such as diabetes mellitus, cardiovascular disease, psychiatric disorder the use of psychiatric (ATC-N06) and hypnotic (ATC-N05) medication, and information on life-style habits (smoking and alcohol consumption) were systematically collected in ***paper II*** and ***III***.

Several well defined methods have been applied in the four papers of this thesis (table 5). They have been discussed in detail below and can be divided in methods to assess sleep and sleep disorders (PG, PSG), subjective assessment of daytime sleepiness (ESS) and objective assessment of sleepiness and cognitive function (MWT, GOSLING, ANT, CTT). Objective data on MVA history were obtained from the STRADA registry (table 5).

Table 4. Anthropometrics and clinical characteristics of subjects included in the final analysis in papers I – IV.

	Paper I	Paper II	Paper III	Paper IV
Population, n	**87**	**1478**	**6984**	**114**
Female:Male n	**26:61**	**438:1040**	**1653:5331**	**29:85**
Age, years	**45.4(10.9)**	**53.6(12.8)**	**51.0(12.1)**	**51.4(12.2)**
BMI, kg/m^2	**27.0(4.2)**	**29.1(5.5)**	**30.7(6.2)**	**30.1(3.9)**
AHI, n/h	**2.3[1.0 – 7.5]**	**10.4[3.2 – 24.2]**	**16.6[5.6 – 37.0]**	**24.8[6.0 – 48.9]**
ODI, n/h	**2.4[1.0 – 7.5]**	**9.1[3.3 – 21.9]**	**10.0[3.1 – 26.4]**	**21.0[5.4 – 40.5]**
ESS score	**7[4.0 – 10.0]**	**10.0[7.0 – 14.0]**	**10.0[6.0 – 13.0]**	**11.0[8.0 – 16.0]**

Abbreviations: BMI=Body-Mass-Index, AHI=Apnea-Hypopnea-Index, ODI=Oxygen Desaturation Index, ESS= Epworth Sleepiness Scale. Data are presented as median [interquartile range] or mean (standard deviation).

Table 5. An overview of main objective and subjective methods used in each of the papers (I – IV).

Paper	PSG	PG	ESS	MWT	GOSLING	ANT	CTT	STRADA
I	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
II		**X**	**X**					**X**
III	**X**	**X**	**X**					
IV	**X**	**X**	**X**		**X**	**X**		**X**

Abbreviations: PSG=Polysomnography, PG=Polygraphy, ESS=Epworth Sleepiness Scale, MWT=Maintenance of Wakefulness Test, GOSLING=Gothenburg Oxford SLeep resistance test, ANT=Attention Network Test, CTT=Compensatory Tracking Task, STRADA=Swedish Traffic Accident Data Acquisition.

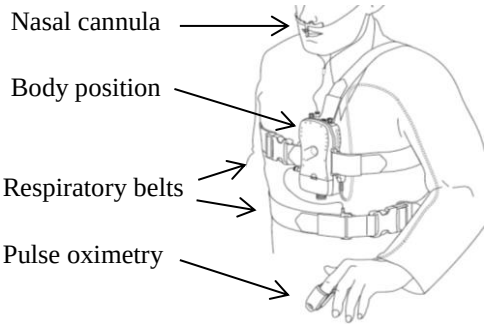
7.2 Objective assessment of sleep and daytime sleepiness

Polysomnography and polygraphy

Sleep was monitored by using ambulatory nocturnal PSG (Embla® A10, Colorado, USA) (table 5). The 12-channel PSG included electroencephalography ((EEG); electrode positions C3/A2, C4/A1, O1/A2, O2/A1), right and left electrooculography (EOG), submental and tibial electromyography (EMG), and electrocardiography (ECG). Furthermore, nasal flow and/or oro-nasal thermistor were used to measure hypopneas, finger pulse oximetry for oxygen saturation and abdominal/thoracic respiratory effort belts for apneas and hypopneas. The apnea-hypopnea index (AHI) was calculated as the number of apneas and hypopneas, with a minimum event duration of 10 seconds, per hour of total sleep. Additionally, hypopneas were scored either when >50% reduction of airflow was followed by a minimum of 3% oxygen desaturation or a ≥4% desaturation was found following a 30% reduction of the airflow. The oxygen desaturation index (ODI, n/h) was defined as the number of at least 4% desaturations per hour of sleep. OSA was diagnosed if the obstructive AHI was ≥5 events per hour of sleep. OSA severity was defined as mild 5-<15, moderate 15-<30 and severe ≥30 events/h (paper I, III, IV). Data recording and analysis of sleep and OSA were performed by an experienced sleep technician according to the 2007 AASM criteria[52, 159].

The polygraphy recordings included standard montage of nasal flow, finger pulse oximetry and abdominal and thoracic respiratory effort belts and a derived snoring signal (Embletta X10 Portable Digital System Embla, CO, USA) (figure 5). AHI was defined as the number of apneas/hypopneas during the recording session defined by lights off and lights on. Polygraphy was assessed (table 5) as a simple and validated objective measure to diagnose OSA[52] and is used as a clinical routine at the Sleep laboratory at Sahlgrenska University Hospital.

Figure 5. Standard polygraphy montage.



In paper 3, sleep and sleep apnea activity has been assessed in the multi-center multinational European database. The protocol allows for the conventionally applied test protocol and data from both PSG and PG may appear in the study. When the AASM 2007[159] scoring criteria were applied per protocol there was an approximately 25% difference in AHI between the PSG and PG recordings[160]. Adequate data quality assurance and data management procedures were applied in the ESADA and our analysis was adjusted for the method used to quantify OSA.

Maintenance of wakefulness and microsleep assessment

Paper I

A modified version of the MWT[161] was performed twice, once in the morning and once after lunch (table 5). The patient was instructed to stay awake during a 30 minute test period. The MWT was used to assess daytime hypersomnolence and the ability to stay awake. The patient was asked to sit comfortably on a bed in a darkened room and to try to stay awake and not to close his/her eyes. Daytime EEG, EMG and EOG were recorded continuously in order to observe episodes of sleep and microsleep[162]. Sleep was defined as 60 continuous seconds of desynchronized EEG with the absence of eye movements. A microsleep event was defined as a minimum of 3 seconds of consecutive theta (saw tooth) pattern in mainly the frontal and central EEG signals[163], and no other obvious evidence of detectable wakefulness, such as eye saccades or body movements. Microsleep events may be more informative than sleep latency in the context of MVA risk since microsleep has been detected in the condition of drowsy driving.

7.3 Subjective assessment of sleepiness, sleep disorders and quality of life

Excessive daytime sleepiness

Subjective daytime sleepiness was assessed by the ***Epworth Sleepiness Scale (ESS)*** to determine general degree of sleepiness over a period of time [152] (table 5). The ESS is a widely distributed and validated instrument employed in sleep apnea research to measure subjective perception of falling asleep during different daytime activities. The subject is asked to score the likelihood to doze off in eight different daily situations on a 4-point scale [164]. The ESS is a debated measure of sleepiness, since it is prone to recall bias. Patients might not recognize or be aware of their sleepiness and underreport their state of sleepiness [165]. However, ESS remains as an important tool to assess subjective sleepiness and the individual perception of sleepiness. In professional drivers it is suggested that the ESS is more likely to be under-scored rather than over-scored as some respondents may attempt to avoid possible medico-legal consequences[166].

Sleep disorders and quality of life

Paper I

Subjective measures of sleep were assessed by means of a ***sleep diary***. The sleep diary addressed subjective quality of sleep, total sleep time, sleep latency and sleep efficiency. The self-administered ***Insomnia Severity Index (ISI)*** was used to assess insomnia symptoms[167] with a validated cut-off threshold of >14 to distinguish moderate to severe insomnia. The ***International Restless Legs Syndrome Scale (IRLSS)*** questionnaire is a scale of ten questions leading to a score ranging from 0-40 and measures the severity of restless legs syndrome (RLS)[168]. A score in the range of ≥11-20 was used to define mild to moderate RLS and a cut-off of ≥21 was used to define severe RLS. The ***Karolinska Sleepiness Scale (KSS)***[154] uses a nine-point scale to measure the current state of subjective sleepiness[169]. A higher point on the scale suggests increased sleepiness. The validated Swedish version of the ***Functional Impact of Sleepiness scale (FIS)*** questionnaire [170] includes 40 questions (score range 0 to 160) and is used to assess symptoms of fatigue in the cognitive, physical, and psychosocial domains. Health related impact on quality of life was assessed using the ***short form 36 (SF-36)*** survey which measures eight different dimensions (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health)[171]. Each scale ranges from 0 (worst health state) to 100 (best health state).

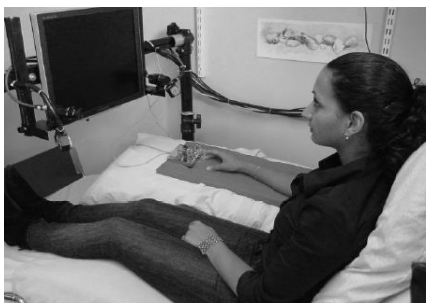
7.4 Assessment of neurocognitive function

Paper I and IV

All neurocognitive tests were performed in a darkened and noise reduced room. The patient was seated in front of a monitor and was not given information on elapsed time (figure 6). The specific neurocognitive tests were selected to reflect simple and complex domains of vigilance, attention and performance during monotony over a period of 20 to 40 minutes, depending on the specific test duration. Microsleep was recorded by means of EEG, EMG and EOG electrodes on the scalp of the subject during the event of neurocognitive tests (paper I).

In paper I, all neurocognitive tests were assessed twice (morning/afternoon) at baseline and during CPAP treatment. The mean neurocognitive test scores from the two sessions were analyzed and presented. In paper IV, study II (RCT cohort) only included morning test sessions and therefore the mean test scores were calculated for all three studies included in paper IV.

Figure 6. Illustration of laboratory test setting (M Karimi, 2014).



The Gothenburg Sleep resistance test (GOSLING)

The GOSLING, a modified version of the Osler (Oxford Sleep Resistance)[148], was developed in our laboratory to overcome the anticipatory response effect that might be expected in the Osler. The 20 minute duration of GOSLING is identical to that of the Osler. However, the subject is instructed to respond to a 1 second low intensity stimulus presented at random intervals of 3 and 10 seconds in contrast to the fixed 3 second intervals of the Osler test[148]. The Gosling can be classified as a simple reaction time test and examines number of lapses and sleep latency under extremely monotonous conditions. Simple reaction time (RT, milliseconds (ms)) is calculated from the speed of response and a missed response (lapse) was scored when the response duration was >2 seconds.

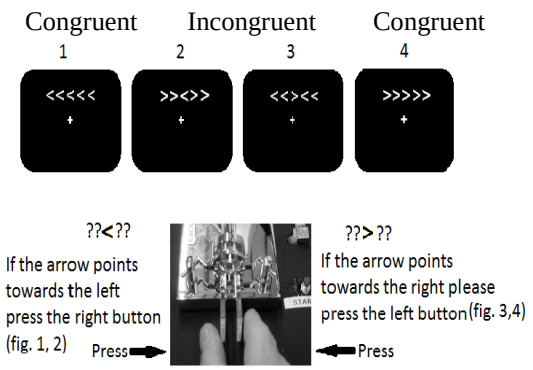
The Attention Network Test

The ANT [123] addresses three dimensions of preconscious attention related to task fatigue:

- *Alerting* – to what extent attention is engaged
- *Orienting* – to what extent attention is disengaged from one focus and redirected towards another
- *Executive processes* – how accurately and efficiently sensory information is interpreted and responded to

Subjects were introduced to a set of 5 arrows (stimulus) either congruent pointing in the same direction as the central arrow or incongruent pointing in the opposite direction (figure 7). In random order, a circle appears (center or spatial cue) immediately prior to when the arrows appear in order to induce an alerting effect. The subject has to recognize the direction of the arrow in the middle and to decide which one out of two buttons to press. The number of lapses and reaction time are determined in order to quantify maintained attention as well as decision making during a period of 27 minutes.

Figure 7. Instructions for The Attention Network Test demonstrating the congruent and incongruent stimuli presented on the monitor.

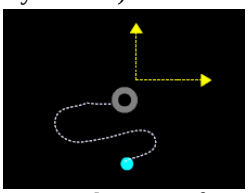


The stimulus is either preceded by a cue (at 200, 400, 600, 800 or 1000 ms) or no cue. By changing the location of where the cue is presented in relation to the central fixation point, either at the location of the upcoming target (spatial) above or below the central fixation point, or at the fixation point subjects were alerted to when but

not where the stimuli could be expected (temporal cue). The alerting effect is measured as RT between no cue and a central cue at 400 ms. The difference in RT between the spatial and the temporal cues defines the orienting effect at 200 ms. Conflict reflects executive function and is defined as the difference in RT between congruent and incongruent stimuli and reflects how accurately and efficiently the direction of the arrows are responded to.

Compensatory Tracking Task

The CTT[131] (paper I) was used to examine the visuo-motor ("eye-hand") coordination and sustained attention among PTOs. The subject is asked to maneuver a disk (7 mm in diameter) on the computer screen using a trackball, keeping it in the center of a circle at a fixed position on the screen. The disk, however, is continually buffered by forces which require continuous user compensation in order to maintain the target position. A mean distance of 1.5 – 2.0 disc radii between the center of the circle and the disk was considered as good performance. A distance greater than 2 disk radii indicated a decline in performance and a tracking error of >9 disk radii indicated poor or no performance. The median distance and the tracking variability as well as duration of lapses in disk maneuver were calculated over 40 minutes.



7.5 Assessment of motor vehicle accident history

Subjective assessment

The history of motor vehicle accidents in PTO´s was assessed in ***paper I*** with an accident questionnaire. The prevalence of MVA (yes/no) during the past year and past five years was determined.

Objective assessment

Motor vehicle accidents assessed in ***Paper II*** and ***IV*** were those recorded in the Swedish Traffic Accident Data Acquisition (STRADA) registry[10], operational since 1999. The registry includes information on more than 500 000 individual road traffic accidents from the entire Swedish national road transport system. The information is reported by the Swedish police and the major emergency hospitals nationwide. Once the police have arrived at the accident site, standardized information is collected for registration in the STRADA. All types of accidents including pedestrians, bicycles and train/tram accidents are reported in the registry. The reported information includes severity and cause of an accident, type of accident and degree of personal and property damage. The degree of personal injury is routinely reported in the STRADA. In this thesis, personal injury was categorized as yes/no.

In ***paper II***, individuals from the general population with a record of at least one MVA during the period 2002 to 2012 and with distribution of community of residency proportional to that of the patient population were included. Accidents that involved tram/train, bicycles or motorcycles were excluded. DL type in the control group was estimated based on existing regional statistics provided by the Swedish transportation agency [10]. Exposure to traffic was assessed by means of self-reported annual driving distance (km) in paper II and III. ***Paper IV*** included MVAs registered in the STRADA during 2001 to 2012 irrespective of community of residency. Accidents caused by vehicles other than motor vehicles were excluded. Exposure to traffic was not available in this population.

An in-depth analysis of causality or the involvement of a possible sleepiness related component in the accident has not been performed within the current thesis.

7.6 Statistics

The statistical analysis in papers I to IV was performed by using PASW Statistics 17.0.2 (SPSS Inc., Chicago, USA). The MVA risk calculated in paper II was performed with R version 2.15.2 (Copyright (C) 2012 the R Foundation for Statistical Computing).

Paper I through IV

Data are presented as mean (standard deviation (SD)) or median [25% to 75% quartile range (IQR)] or median [minimum – maximum range]. A two tailed p value of < 0.05 was considered significant. All statistical methods used in this thesis are listed in table 6.

For non-parametric independent samples Kruskal Wallis H test was used. The Mann-Whitney U-test was used for between group differences and ordinal scale data such as the ESS and for comparison. Pearson´s Chi-square was used to assess associations between quantitative data with an expected frequency of greater than 5 in each cell. The Games-Howell Post Hoc test was used as a robust measure to analyze regional differences among categorical risk factors. Binary logistic regression was used for categorical response variables, applying the enter method, predictors were either independent categorical or continuous. Stepwise backward and forward likelihood-ratio methods were used to test each predictor. Where applicable, predictors were analyzed as a categorical or as a continuous variable for the best model fit. The year of diagnosis was included as a variable in order to control for the time effect on the incidence of MVA. A multivariable logistic regression analysis was performed to examine the extent of injury (yes/no) among patients adjusted for age, year of accident and gender.

Paper I investigated the prevalence of sleep disorders among a group of PTO´s and the prevalence was assumed to be according to the prevalence reported in the general population (between 9 and 24% females and males[66], respectively) with OSA. A formal power calculation was not performed for the interventional study in paper I due to the unknown prevalence of OSA in this particular PTO population. In paper II, power calculation is described in the section below. Paper IV was a pilot study of the new methods used for MVA risk prediction.

Table 6. Statistical methods used in Paper I through IV.

Statistics	Paper I	Paper II	Paper III	Paper IV
Categorical data test				
Pearson´s Chi-square		**X**	**X**	**X**
Poisson distribution		**X**		
Non-parametric test				
Kruskal–Wallis	**X**		**X**	
Spearman's rho correlation	**X**		**X**	
Mann-Whitney U test		**X**	**X**	**X**
Post-Hoc test				
Games-Howell			**X**	
Logistic regression test				
Binary logistic		**X**	**X**	**X**

Specific considerations for estimated risk analysis in Paper II

In order to adjust for potential confounding factors of MVA risk, traffic environment and density as well as road conditions were accounted for. Accordingly, the patient and control groups were stratified for residency (n=9 regional metropolitan or suburban areas within hospital capture area). Further stratification was performed accounting for age class (18-19, 20-24, 25-34, 35-44, 45-54, 55-64, 65-74 and 75-80 years), and driver´s license type (A/B or C/D/E) generating 144 subgroups for each calendar year. Based on these groups the final estimated risk analysis included 74 out of the 82 patients with a positive MVA history. Information on residency was missing in eight patients and they were excluded from the risk analysis.

Based on available literature data on a 2-11 fold increased risk of MVA in patients with OSA[29] it was assumed that a 2 -3 times increased in MVA risk would be observed. A one-sided statistical hypothesis tests were conducted at a confidence level of 5%, to test whether more MVA's had been observed in the patient cohort than in a respective control group (before and after diagnosis or in total). Under the null hypothesis, it was assumed that the number of MVA's was Poisson distributed and that there was no difference between the patient cohort and the control group. The Poisson distribution may be motivated as conservative conditioning on the yearly number of accidents in each subgroup.

A parameter estimate for the expected number of MVA's in the control group was generated. The probability of having an MVA was estimated for each subgroup and each year using registry data. The respective probabilities were multiplied by the number of patients in each subgroup for each year and accumulated. The null hypothesis assuming no difference between groups was rejected if the number of observed MVA's in the patient cohort was found to be larger than the 95% quintile of a Poisson distribution, having the estimated expected number of MVA's in the control group as its parameter. The observed number of accidents in the patient group was compared with the estimated number in the control group. The accidents for patients and controls were categorized into three age groups accumulated and weighted by each subgroup size.

The independent influence of medical conditions and factors previously proposed to influence traffic safety including age, gender, OSA severity (AHI), diabetes mellitus, alcohol consumption, daytime sleepiness (ESS), short sleep time (≤5 hrs/night), driving distance, DL type (C/D/E) and use of hypnotics/psycho-analeptics, were added in the model. Stepwise backward and forward likelihood-ratio methods were used to test each predictor for the best model fit and adjusted for the year of diagnosis. Variables with a large difference in scales (e.g. km/year) and units were standardized and transformed to their z-score.

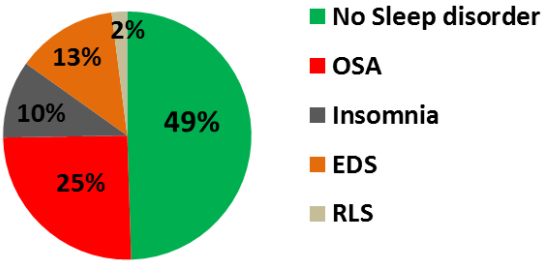
The time window for CPAP compliance was assessed by calculating the number of follow up days for each patient entering the study (2007 to 2012). The incidence of MVA per 1000 individuals per year was then calculated 5 years before diagnosis (2002 to 2007) and for the time after start of the CPAP therapy.

8 RESULTS AND DISCUSSION

Prevalence of sleep disorders and daytime sleepiness

A sleep related disorder such as insomnia, hypersomnia, or restless legs syndrome was present in more than 50% of PTO´s (figure 8) (paper I). In this group, 25% of PTO´s were diagnosed with OSA and 13% complained of excessive daytime sleepiness. This high prevalence of sleep disorders was comparable with that reported in similar age strata of the general population[172].

Figure 8. The prevalence of sleep disorders among public transport operators (PTO) (paper I).

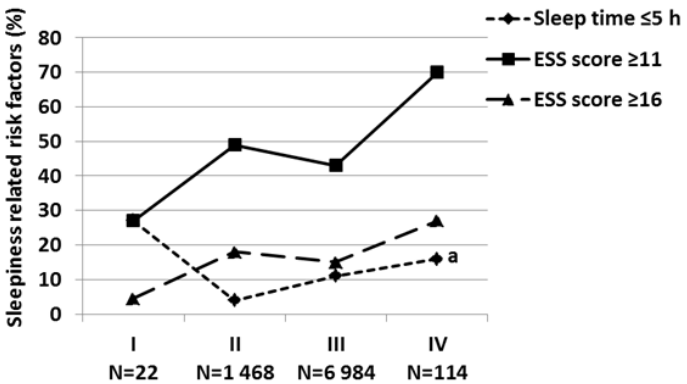


Abbreviations: OSA=Obstructive Sleep Apnea, EDS=Excessive Daytime Sleepiness, RLS=Restless Legs Syndrome.

The prevalence of subjective complaints of EDS differed between the populations investigated in this thesis (papers I-IV). An Epworth score of ≥11 was found in 28-70% of subjects in the four cohorts and severe EDS (ESS ≥16) was reported in 3-28% of study participants. Of note, only one out of 22 PTO´s diagnosed with OSA reported severe EDS. Conversely, short habitual sleep time (≤5 hours per night) was more prevalent among the PTO´s compared with the other three cohorts studied in this thesis (figure 9). Although the study sample is small, EDS and severe EDS appeared to be more prevalent compared with studies of the general population[173]. The prevalence of short sleep time, on the other hand, matched that of several population based reports[174, 175]. Arnold et al.[176] demonstrated that short sleep time (less than 6 hours) was associated with a 40% increase in sleepiness related traffic events, such as nodding-off while driving. In addition, Stoohs et al.[14] found a

significant association between frequency of crashes and subjectively reported EDS. Commercial drivers with self-reported EDS had a three times higher frequency of accidents when compared with drivers without EDS [14]. Our functional data suggest that commercial drivers like PTO´s frequently suffer from EDS but that this in part may be unrecognized because PTO´s tend to systematically underreport EDS, which has been previously reported [166].

Figure 9. Excessive daytime sleepiness and short habitual sleep were common but varied between the different cohorts in this thesis.



[a] *Note that sleep time was based on total sleep time determined by PSG in paper IV.*

Sleepiness and short habitual sleep time have become a concern in our 24h society because they are associated with poor health, work-related problems and reduced quality of life[177, 178]. A survey in the working population Kuppermann et al.,[177] reported on reduced health related quality of life and more frequent work-related problems in subjects with sleep disorders[177]. The PTO´s with sleep disorders in paper I reported a lower quality of life in 5 out of 8 domains of the SF-36 including physical functioning (p=0.06), role-physical, social functioning, role emotional, and mental health, all p≤ 0.01, respectively. It is not unlikely that poor awareness of health is overrepresented among those with sleep disorders. In fact, an unhealthy lifestyle, including smoking and increased alcohol consumption was more common among European frequent drivers evaluated for OSA in paper III. The findings suggest that identification of individuals at risk of MVA, even in patient cohorts, should include not only an assessment of OSA or EDS, but also lifestyle factors in a more general sense. Similarly, short habitual sleep time and intake of hypnotics may

be important life style factors to be addressed in the clinical assessment of OSA patients. Short sleep time was particularly prevalent among patients in western European countries (15.5%) and 10.8% of patients in the northern region used hypnotic medications (paper III). This suggests that assessments of these potential risk factors should be made for identification of clinical OSA patients at MVA risk.

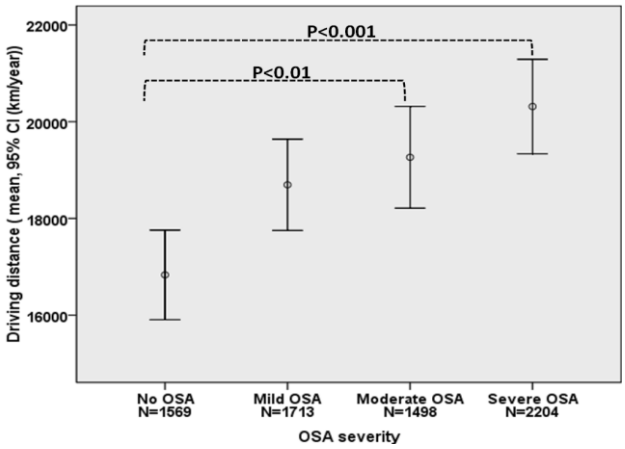
Exposure to traffic in OSA

Exposure to traffic as an important MVA risk factor was determined by means of self-reported annual driving distance and 49.7% of patients were found to exceed 15,000 km in the ESADA cohort (paper III). The lowest frequency was reported in patients from the western region of Europe (40.9%), whereas frequent driving (≥15 000 km) was most prevalent among patients from the central region (55.4%). According to interviews with European citizens reported in the Special Eurobarometer [16] 50% drive between 5,000 and 15,000 km per year. The regional distribution of this particular driving distance class was similar that found in the ESADA. For instance, a distance between 5,000 and 15,000 km was reported by 58% of drivers in Germany, 55% in Italy, 51% in France and 47% in the UK. However, an even longer driving distance (≥ 30,000 km/year) was reported by 6% of the EU drivers while in the ESADA cohort of patients with OSA long distance driving was overrepresented and reported by 19% of patients. The fact that long-distance driving was overrepresented in clinical OSA patients may reflect a referral bias as doctors are more likely to refer a sleepy long-distance driver for clinical evaluation. It may also reflect a higher awareness and experience among long distance drivers of the safety hazard associated with sleepy driving and a higher proneness to seek medical attention.

Several studies have reported on excessive daytime sleepiness among commercial drivers[14, 92, 179]. In our data, PTO´s with a history of a traffic accident were sleepier during daytime compared with those without accident (paper I). Further, among OSA patients long driving distance (≥ 30,000 km/year) was found to be associated with a 1.28 fold increased odds (95% CI [1.01–1.63] p=0.04) for severe EDS (ESS score >=16) (paper III). A possible explanation for increased EDS in long distance drivers may be poor sleep habits evidenced by a shorter habitual sleep time. In fact, detailed analysis of our data in long distance drivers, compared with patients driving less than 30,000 km/year, showed that the mean habitual sleep time was somewhat shorter (6.7 vs. 7.0 hours, p<0.001) (paper III). In addition, short habitual sleep time tended to associate with severe daytime sleepiness (OR 1.22 [0.99–1.49], p=0.06) and a similar weak trend was seen between the mean ESS score and self-reported driving distance (p=0.07) (paper III). Notably, 37% of the OSA patients in the long distance group were diagnosed with severe OSA (AHI ≥30 n/h) (figure 10). To our knowledge, the overrepresentation of long distance drivers in a large clinical OSA cohort has

previously not been reported. This finding has obvious implications for diagnostic and therapeutic procedures as both factors have been reported to be associated with increased MVA risk [97].

Figure 10. Annual driving distance in frequent drivers (≥15000km) relation to OSA severity in clinical European OSA patients (paper III).



History of motor vehicle accidents among OSA patients

MVA´s were found in 5-10% of clinical patients (paper II and IV) and in 59% of PTO´s diagnosed with OSA (paper I). The difference between groups reflects the definition used for MVA classification. In paper II and IV we used a record of a MVA during the past 5 years in the STRADA registry, whereas in paper I self-reported information was derived from a questionnaire. The risk of MVA was 2.5 times higher in OSA patients compared with controls ($p<0.0001$) in paper II. A gradual decrease in the observed estimated risk for MVA was found between three age classes. The strongest relative influence of OSA on MVA risk was found in the oldest age class (ratio 2.6, 2.4 and 3.5 respectively, figure 11) (paper II). Our findings mirror previous studies demonstrating an increased risk of MVA in OSA. A meta-analysis by Tregear et al. pooled data from ten different studies[14, 91, 95, 97, 98, 101, 102, 113, 149, 180] and reported a 2.43 (CI [1.21–4.89], p=0.013) fold relative risk of MVA in OSA patients. Stoohs et al. reported on the prevalence of MVA among commercial truck drivers and found a doubling of accidents frequency in drivers with OSA. These results are in line with our data in PTO´s who exhibited a relative risk of 1.4 – 2.2 among PTO´s with OSA (figure 12).

Another interesting aspect of our evaluation of MVA´s in the STRADA registry relates to the risk of physical injury associated with the accident. In paper II it was demonstrated that the risk of injury was 1.9 times higher among patients compared with controls ($p<0.01$). This finding suggests that not only accident rate but also consequences of MVA´s in general may be more severe than in other types of accidents. Future studies including an in-depth analysis of accidents may shed further light on this possibility.

Figure 11. The number of observed and estimated MVA's in patients with OSA and in the control group, respectively (paper II).

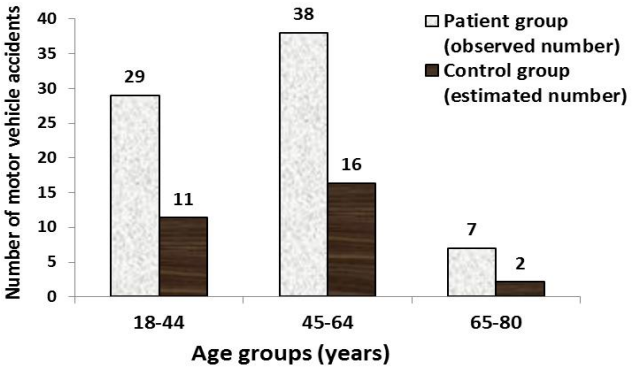
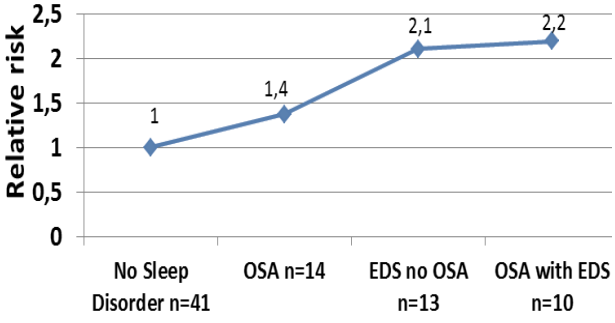


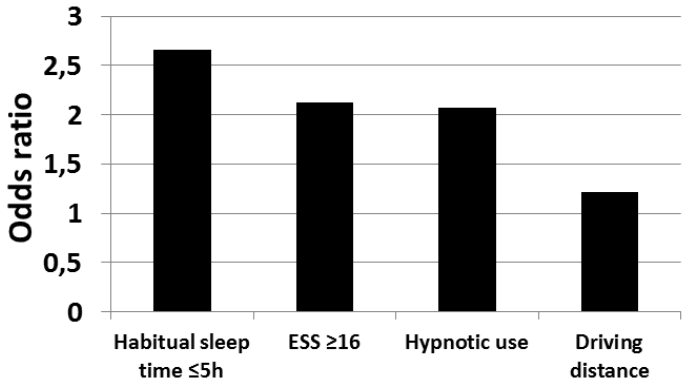
Figure 12. The relative risk of traffic accidents among public transport operators with Obstructive Sleep Apnea (OSA) and subjective Excessive Daytime Sleepiness (EDS) with reference to those without a sleep disorder (paper I).



Clinical risk factors of MVA in OSA

The contribution of various risk factors for MVA was assessed in multivariable logistic regression models. In paper II, we found significant associations between a MVA history and short habitual sleep time (≤5 hours per night), ESS score ≥16, use of hypnotic medication, and annual driving distance (OR 2.66, 2.13, 2.07, 1.22, respectively, p≤0.03) (figure 13). Additionally, young age was associated with a 2% higher odds for an MVA (p=0.05) (paper II). Interestingly, several other characteristics previously proposed to influence traffic safety including gender, OSA severity (AHI and ODI), diabetes mellitus (DM), and alcohol consumption were not associated with MVA history in our study sample.

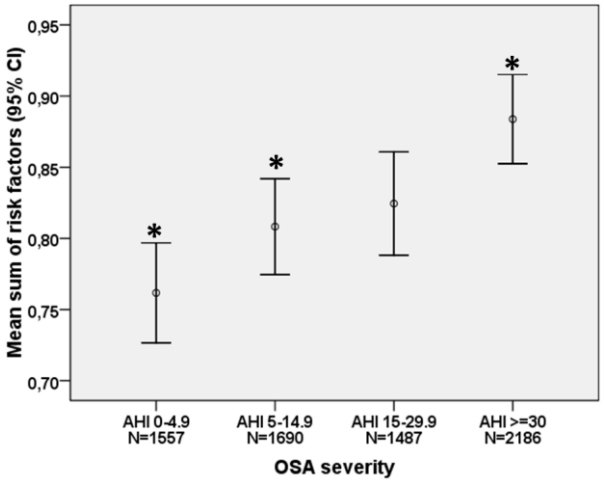
Figure 13. Risk factors validated in paper II and their association with MVA history. Shown is the odds ratio for a history of MVA associated with various risk factors in patients with obstructive sleep apnea (paper II).



Abbreviations: ESS=Epworth sleepiness scale.

The sleepiness related risk factors (short habitual sleep time, use of hypnotics high ESS score) and annual driving distance identified to associate with MVA history in paper II, were further analyzed in detail in paper III. The mean number of risk factors was found to increase in relation to sleep apnea severity (figure 14).

Figure 14. Mean number of validated risk factors in relation to OSA severity.



*Statistics: ***** P<0.01 for multiple comparisons of AHI ≥30 n/h vs. AHI 5-14.9 n/h and AHI 0-4.9 n/h (paper III).*

A sensitivity and specificity analysis addressing conventionally used markers of symptomatic OSA was applied to determine their predictive value for MVA risk. The sensitivity and specificity for excessive daytime sleepiness (ESS score ≥11) was only 55% and 6.9%, respectively. Similarly, the sensitivity and specificity for severe OSA (AHI ≥30 n/h) was 18% and 6%, respectively (table 7).

Table 7. Sensitivity and specificity analysis using conventional markers for severe OSA (AHI ≥30 n/h) and daytime sleepiness (ESS ≥11) for MVA prediction in OSA patients.

	MVA n=81	**No MVA n=1325**	**Sensitivity**	**Specificity**
ESS score 0-10	36	676	44%	5.8%
ESS score ≥11-24	45	649	55%	6.9%
	N=76	**N=1178**		
AHI <30 n/h	62	943	82%	6.6%
AHI ≥30 n/h	14	235	18%	6.0%

Abbreviations: MVA=Motor Vehicle Accident, ESS=Epworth Sleepiness Score, AHI=Apnea Hypopnea Index (paper II).

We used a separate sensitivity and specificity analysis to evaluate if the accumulated number of sleepiness related MVA risk factors identified in paper II may be used to identify patients with a MVA history (table 8). In general, the sleepiness related risk factors had only a limited sensitivity and specificity for identification of patients with a MVA history. For instance, sensitivity and specificity in a patient with ≥1 risk factor was 45 and 9.1%, respectively (table 8).

Table 8. Sensitivity and specificity analysis of validated risk factors ((RF), Epworth sleepiness score ≥16, habitual sleep time ≤5hours, use of hypnotics (yes/no), annual driving distance ≥15000 km) associated with motor vehicle accidents (MVA) among clinical OSA patients (paper II.)

Tentative cut-off	MVA n=81	No MVA n=1406	Sensitivity	Specificity
≥0 RF	81	1406	100%	5.8%
≥1 RF	37	408	45%	9.1%
≥2 RF	6	30	7.3%	16.7%
3-4 RF	2	0	2.4%	100%

Our data jointly suggests that several previously described risk factors for MVA including short sleep time, use of hypnotics, high Epworth sleepiness scale score and frequent annual driving could be linked to a history of MVA in OSA patients occurring in the STRADA registry. However, the sensitivity and specificity of these factors for prediction of risk proportionally low. Traditional measures of OSA severity were even poorer in terms of prediction of accident risk. These components, which correspond to what conventionally is presented to clinicians in terms of information is clearly insufficient for clinical medicolegal decision making in OSA. Interestingly, to our knowledge, a sensitivity and specificity analysis of the predictive value of the widely used Epworth sleepiness scale to detect OSA patients at risk of sleepiness related accident has never been performed. Neither is there any information available in terms of accident risk prediction on factors like short sleep time, use of hypnotics, frequent driving or the OSA related markers AHI and ODI. Hence, there is a need for additional functional assessment of driving capacity in this patient group. A general limitation in studies dealing with accident registries resides in the fact that only a limited proportion of accidents are causally associated with sleepiness and cognitive function. Future studies need to address an in-depth analysis

of accidents in order to sharpen the association between MVA history and different dimensions of OSA.

Functional risk factors of MVA in OSA

In paper I and IV we attempted to introduce various functional measures of reduced attention, alertness, and executive function and to evaluate their value as predictors of actual accident risk. Simple measures of attention in the ANT test, defined as the number of responses, were found to be useful to discriminative between OSA patients with and without a history of MVA (table 9). A specific dysfunctional cognitive component, potentially associated with OSA, may reflect increased proneness to neglect and accident risk. Interestingly, we identified a dimension of complete lapse of attention, which was markedly different between patients with and without a history of MVA. This suggests that the design and character of the neurocognitive function test may be further refined to even better reflect the behavior in the driving condition. Interestingly, no complex measure of attention in the ANT, including orienting and alerting capacities as well as executive capacity, was found to differ significantly between OSA patients with and without a MVA history.

Table 9. A comparison between number of lapses and responses to stimuli in the attention network test (ANT) among OSA patients with or without a history of MVA (paper IV).

ANT	MVA (n=11)	No MVA (n=103)	P-value
Lapse, n	42 [5–121]	5 [1–25]	0.02
Response, n	238 [158–272]	271 [256–277]	0.03

Statistics: data are presented as median [Interquartile range], non-parametric Mann Whitney U test was performed for between group differences.

To our knowledge, this is the first study to apply the ANT in order to examine sustained attention and the predictive value of this method in an OSA patient cohort. The findings clearly encourage further detailed evaluation of the value of this method in the context of MVA risk assessment. Matchock and co-workers[181] demonstrated that the three attentional domains of the ANT may be affected by time-of-day as well as chronotype. The alerting effect was impaired in the afternoon/evening among morning-type subjects and the executive function showed a midday drop in both chronotypes. The orienting effect was unaffected by time-of-day or chronotype[181]. We were not able to detect differences in these domains of the ANT in our study and this may be explained by that the time-of-day and chronotype factors were not fully explored in our experiments. Papers I and IV assessed the ANT at two occasions, in

the morning (around 09.00) and midday (around 13.00). Since no systematic difference in performance was found (data not shown) all ANT variables were averaged.

Simpler measures of attention such as reaction time and number of lapses were assessed in the GOSLING test. There were differences in several of the variables between patients with and without a MVA history (table 10). Median reaction time was longer and variability in performance was higher in patients with an MVA. The total numbers of lapses as well as the consecutive number of lapses were also increased (table 10).

Table 10. Between group differences in the GOSLING related variables among OSA patients with and without a history of MVA.

GOSLING	MVA (n=9)	No MVA (n=83)	P-value
Median RT, ms	462 [393 – 551]	407 [361 – 449]	0.05
RT variability, ms	512.2 [415.1 – 580]	448 [387 – 495]	0.04
RT IQR, ms	175.0 [102.5 – 200]	112 [84 – 141]	0.03
Missed trials, %	0.2 [0.03 – 0.31]	0.02 [0.01 – 0.06]	0.01
Missed lapses, n	29 [10 – 97]	7 [2 – 19]	0.01
Consecutive lapses, n	15 [5– 46]	6 [2 – 14]	0.03

Abbreviations: MVA= Motor Vehicle Accident, RT=Reaction Time, ms=Millisecond, IQR=Interquartile Range (paper IV). Statistics: data are presented as median [Interquartile range], non-parametric Mann Whitney U test was performed for between group differences.

Jointly, the findings suggest that sustained attention was impaired in a subgroup of OSA patients and that the performance in simple reaction time tasks may distinguish between OSA patients with and without a MVA.

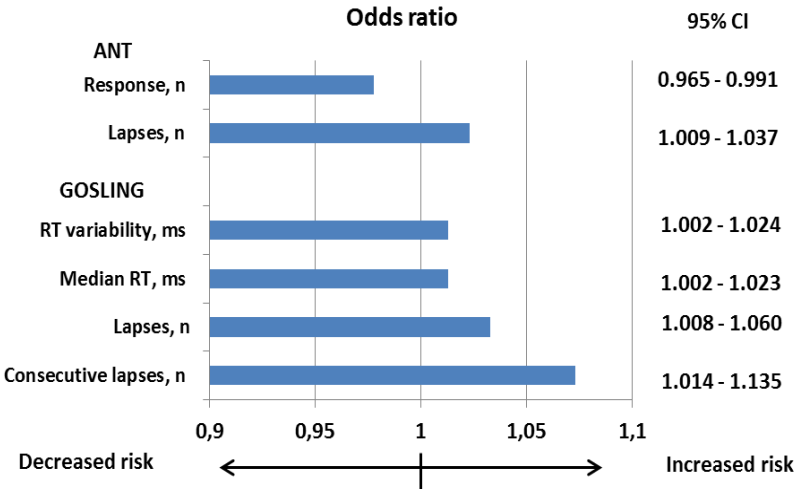
The ANT and GOSLING data were independently analyzed for MVA risk in a logistic regression, adjusted for gender, age, excessive daytime sleepiness (ESS ≥11) as well as OSA severity (AHI n/h). In the ANT, there was a positive association between the number of lapses and MVA history, which was mirrored in the association found between the decreased number of responses and MVA history (figure 15). Hence, the odds ratio for a MVA history was significantly increased when analyzing attention in the GOSLING. An increase in median reaction time (ms)

as well as the variability (ms) in sustained attention, as well as total and consecutive number of lapses were all positively associated with an increased MVA risk (figure 15). Thus, a 10 millisecond increase in the GOSLING reaction time was associated with a 13% increase of MVA risk. In the ANT, each "number of response" unit was associated with a 2.3% MVA risk reduction.

The consecutive number of lapses in the GOSLING was associated with an increased risk of MVA (figure 15) (paper IV). This is particularly noteworthy since the design of the GOSLING test originally was based on the OSLER test [148]. The OSLER which also records the number of consecutive lapses has been validated against the MSLT[148].

Taken together our data suggests that dimensions of sustained attention in at least two types of cognitive tests were modified in OSA patients with a record of previous MVA. The sensitivity and specificity of these measures alone remain proportionally limited but will need further evaluation. Studies addressing MVA risk may need to integrate a functional risk factor and traditionally recognized risk factors in order to provide useful tools for recognition of OSA patients at particular risk for MVA.

Figure 15. Odds ratios for risk of MVA and 95% confidence intervals (CI) of neurocognitive test variables in the Attention Network Test (ANT) and the Gothenburg Oxford Sleep resistance test (GOSLING) in patients with OSA.

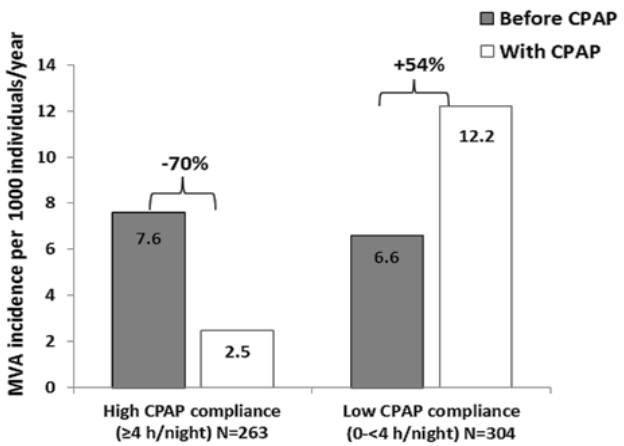


CPAP treatment and MVA risk

Objective and subjective measures of sleepiness and neurocognitive function were assessed before and during treatment of sleep apnea (CPAP n=10, OA n=2) in PTO´s. Mean CPAP compliance was 4.3(1.5) hours/night. In the larger group of clinical patients (n=567) mean CPAP compliance was 3.8(2.6) hours/night (paper II). High CPAP compliance (≥4 h/night) among clinical patients was associated with a 70.0% reduction in MVA incidence (per 1000 individuals/year) (figure 16). In paper II, which covered a follow-up period between 2007 and 2011, it was noted that the overall background accident rate in the STRADA registry decreased with approximately 15.9% during the corresponding time period. It has been stated that this rapid reduction in accident rate is related to general measures (e.g. speed limits, road constructions etc.) to obtain a decrease of accident rate[10]. This reduction is likely to have affected our results, but it cannot explain the reduction of accident rate demonstrated in the CPAP treated patients. Our findings are in line with previous findings[89, 97, 101, 102, 107] and support a causal relationship between OSA and MVA risk.

Neither the current nor previous studies in the field have been able to document a dose-response relationship between OSA severity and MVA risk. Only two[89, 102] previous studies, both addressing smaller populations, used objective accident data in their evaluation. Moreover, no previous study addressed the important issue of objectively assessed treatment compliance. In our study, patients with a CPAP compliance ≥4 h/night were slightly more obese, had shorter sleep latency, higher AHI and reported a slightly higher annual driving distance. This suggests that high CPAP compliance was more likely in patients with more severe OSA, but the association between disease severity and CPAP use was generally weak (paper II).

Figure 16. The incidence of MVA per 1000 individuals/year before and during CPAP treatment was compared in OSA patients with high or low CPAP compliance.

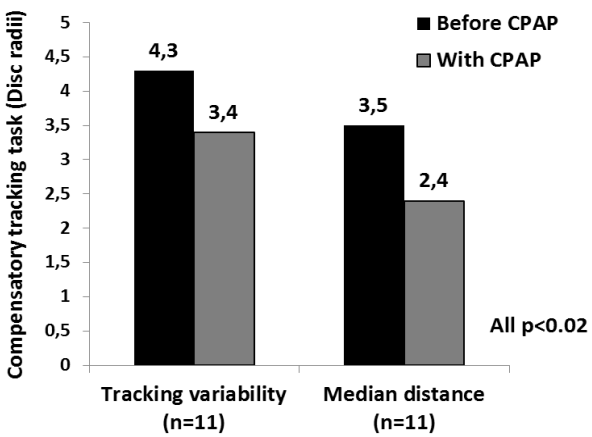


EEG verified microsleep and daytime sleep latency (MWT) was performed in the PTO´s (paper I). In the MWT, mean sleep latency tended to increase following CPAP treatment (26.7(7.9) to 30.0(3.8) minutes, p=0.06). In addition, the number of microsleep events during neurocognitive testing as well as the MWT were reduced following treatment (median [IQR] 9 [0-20.5] vs. 0 [0-17.5], p=0.001 (paper I). Measures of subjective daytime sleepiness, the ESS score, the KSS and the FIS score decreased following treatment (paper I).

Although the mean sleep latency assessed in the MWT was within the normal range (0-<20 min), treatment resulted in a reduction of both objective and subjective sleepiness. The long sleep latency found among PTO´s suggests that professional drivers might have developed strategies to combat sleepiness during monotony. Our findings on the effect of CPAP on daytime sleepiness are in line with previously reported data[107,108]. Following sleep apnea treatment, Sangal et al., found an improvement in the ability to stay awake in the MWT but this was not reflected in the MSLT[182]. Our findings may be clinically relevant as short MWT sleep latency in OSA patients has been found to associate with performance deficits in a driving simulator[183].

The compensatory tracking test was assessed in order to determine visuo-motor performance before and during CPAP in paper I. The tracking variability and median distance measures were significantly improved with treatment (figure 17). This may suggest a better sustained performance after CPAP possibly as a result of less visuo-motor impairment which has been shown elsewhere to be associated with OSA[136]. Unfortunately, we were not able to validate this finding in paper IV as the test algorithm did not include CTT in two of the three study protocols.

Figure 17. Performance measured as tracking variability and median distance (disk radii) in the CTT before and with CPAP treatment among public transport operators (paper I).



Study limitations

Paper I

A pre selection bias in the recruitment process cannot be excluded as study participation was voluntary and it may be expected that subjects fearing restrictions on continued employment may have hesitated to participate in the study. Moreover, measures of performance and attention assessed in a laboratory environment may not compare with real life situations and may not be adequate to detect impairments that reflect every day risk – in this case traffic accidents. Finally, due to ethical reasons, our intervention did not include a randomized control group. Given the professional driver status of the study participants this would have raised concerns on traffic safety which usually constitutes an exclusion criterion in randomized OSA treatment studies.

Paper II

It cannot be excluded that this cohort of clinical OSA patients seeking medical attention oversampled individuals who have experienced sleepiness behind the wheel, a near miss accident or even an actual MVA. Data may therefore not be generally extrapolated to reflect the impact of sleep apnea on traffic safety in general. However, the MVA frequency did not accumulate directly prior to the referral for sleep testing. Furthermore, data on actual annual driving distance and degree of daytime sleepiness in the general population subsample is incomplete. Finally, excessive sleepiness was defined by means of the ESS and may be prone to recall bias and a systematic underestimation particularly in commercial drivers. Therefore, these factors are likely to increase variance in the statistical models used to predict MVA risk in OSA.

Paper III

Limitations include the lack of information on actual MVA history for the majority of the patients in the cohort. Self-reported driving distance contains an element of uncertainty. Finally, sleepiness in the ESADA was subjectively assessed.

Paper IV

The study population included subjects with a wide range of OSA severity and clinical symptoms. In addition, we oversampled professional drivers with high traffic exposure which increased the clinical relevance of our findings. As expected, the majority of MVAs were observed among professional drivers but attention deficits were not confined to this group. The finding of prolonged reaction times and increased numbers of lapses was not confined to professional drivers. Further, it is recognized that traffic exposure, often assessed as self-reported annual driving

distance, represents an important risk factor for MVA. However, our study aimed to investigate the feasibility of two neurocognitive function tests to identify OSA drivers at risk for MVA, not to assess risk factors for MVA in the OSA population. Future prospective studies are needed to determine the diagnostic capacity of the GOSLING and ANT tests in an unselected OSA population. Finally, in the current study we did not perform an in-depth accident analysis as it is unknown whether any particular type of accident is associated with OSA in a specific manner.

9 CONCLUSION AND FUTURE PERSPECTIVES

Our study, which in part is based on national accident statistics, supports the notion that untreated OSA increases the risk of MVA. An important mediator of this risk is functional deficit related to daytime sleepiness. Apnea events or subjectively assessed sleepiness do generally not predict MVA risk but CPAP treatment leads to considerable risk reduction. Identification of individuals at risk of MVA therefore remains as a challenge in the management of OSA patients. Importantly, CPAP patients not complying with therapy may require specific attention in the clinical assessment of MVA risk.

European sleep centers encounter a substantial number of patients with a high annual driving distance in combination with a diagnosis of moderate to severe OSA. In fact, our data strongly indicate that frequent drivers may be overrepresented in clinical OSA populations. It seems plausible that novel measures of cognitive function in combination with recognized MVA risk factors (sleepiness and non-sleepiness related) may provide a framework for future individualized MVA risk assessment in patients with OSA.

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