European Respiratory Society statement on sleep apnoea, sleepiness and driving risk

Sleep Apnoea, Sleepiness and Driving Risk. ERS Task Force Report

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Abstract

Obstructive sleep apnoea (OSA) is highly prevalent and is a recognised risk factor for motor vehicle accidents (MVA). However, effective treatment with continuous positive airway pressure has been associated with a normalization of this increased accident risk. Thus, many jurisdictions have introduced regulations restricting the ability of OSA patients from driving until effectively treated. However, uncertainty prevails regarding the relative importance of OSA severity determined by the apnoea-hypopnoea frequency per hour and the degree of sleepiness in determining accident risk. Furthermore, the identification of subjects at risk for OSA and/or accident risk remains elusive. The introduction of official European regulations regarding fitness to drive prompted the European Respiratory Society to establish a Task Force to address the topic of sleep apnoea, sleepiness and driving with a view to providing guidance to clinicians involved in treating patients with the disorder**.** The present report evaluates the epidemiology of MVA in patients with OSA, the mechanisms involved in this association, the role of screening questionnaires, driving simulators and other techniques to evaluate sleepiness and/or impaired vigilance, in addition to the impact of treatment on MVA risk in affected drivers.

Introduction.

Obstructive sleep apnoea (OSA) is highly prevalent with recent general population studies indicating that almost 50% of adult males have moderate or severe sleep disordered breathing (SDB) as measured by an apnoea or hypopnoea frequency per hour (AHI) of at least 15 (1). The clinical syndrome of OSA, based on an AHI of at least 5 along with appropriate daytime symptoms, especially excessive daytime sleepiness (EDS), is reported in up to 10% of the adult male population with about half that prevalence in females (2). EDS while driving is an important factor in motor vehicle accidents (MVA) or work-related accidents. Disorders associated with sleep disturbance and sleepiness are established factors in increased accident risk (3, 4), and OSA is the most prevalent medical disorder associated with EDS. The medicolegal consequences of OSA principally relate to accident risk from OSA with its associated economic implications and legal consequences.

Several jurisdictions have implemented regulations that restrict the ability of patients with OSA to drive until effective treatment is demonstrated (5). These regulations should include both objective severity of OSA demonstrated by measuring the extent of SDB in a diagnostic sleep test and also the level of sleepiness, which is usually assessed in clinical practice by the Epworth Sleepiness Scale (ESS) (6). The importance of including both variables is underlined by the poor association between AHI in a sleep test and the subjective sleepiness measured by the ESS (7, 8), in addition to the continuing uncertainty regarding the relative importance of SDB severity and level of sleepiness in predicting accident risk (9).

In 2014, the European Union implemented a Directive that introduced regulations regulating fitness to drive in patients with OSA. This Directive specifies that patients with AHI $\geq$15 and associated sleepiness should not drive until effectively treated and physician certification is required to confirm suitability to continue driving (10). However, considerable uncertainty prevails among clinicians about this evaluation (11), which likely reflects current uncertainties regarding the evaluation of disease severity, particularly the evaluation of sleepiness. The overarching objective of this Directive is to prevent patients with untreated OSA who report sleepiness while driving from continuing to drive until the disorder is effectively treated.

As a result of the EU Directive and associated uncertainties regarding implementation, the ERS established a Task Force to address the topic of sleep apnoea, sleepiness and driving with a view to providing advice to clinicians involved in treating patients with the disorder.

General Methods

The Task Force members represent a cross-section of experts drawn from the ERS and European Sleep Research Society (ESRS) membership with established interest/expertise in the topic of driving and OSA. The membership included representatives predominantly from respiratory-sleep medicine, but also from neurology, psychiatry, and public health. A patient representative was also included. Members were assigned to working groups within the TF covering the relevant topics of Epidemiology, Mechanisms, Screening, Diagnosis, and Treatment. The work of each working group was predominantly by email and teleconference interactions, and physical meetings of the full Task Force were held during the annual ERS Congresses. Each working group prepared a report, which was integrated into a final report by the Task Force Chairs together with a writing committee.

A combined computerized and manual systematic database search of medical literature was performed, and the respective publications were retrieved from electronic search engines. Reference lists were thereafter systematically examined for relevant articles. Keywords were selected that were appropriate for the relevant working group such as “CPAP” and “DRIVERS”. Then appropriate search words such as “accidents,” “collisions,” “quality of life”, “cognitive impairment”, “vigilance”, “fatigue”, “drowsiness” and “depression” were added.

The main inclusion and exclusion criteria were: published in English; data on human subjects; no reviews, guidelines or case reports. All studies were identified that were relevant to the respective working group, e.g. the evaluation of the effect of nasal continuous positive airway pressure (CPAP) on OSA patients with respect to real and/or near miss road traffic accidents or performance in the driving simulator, sleepiness, quality of life, cognitive function, vigilance, fatigue, drowsiness and depression. Data were independently extracted and analysed, and individual study quality was assessed. All searches were updated in mid-November 2019.

Individual studies were evaluated according to the “Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)‘‘ (**Table 1, e-supplement**), as reported in the Tables.

The present ERS Statement combines an evidence-based approach with the clinical expertise of the TF members, based on a two-step discussion process: first within subgroups focusing on different sections, second in the whole group. When assessing the full body of evidence supporting each statement, we used the grades A-D (**Table 2, e-supplement**). This Statement aims to provide an overview of the literature and current practice and does not make specific recommendations for clinical practice.

Epidemiology of motor vehicle accidents in patients with obstructive sleep apnoea.

Search Criteria

A search on PubMed using the terms: "sleep apnea" AND epidemiology AND driving retrieved 166 references. Fifteen additional records were identified, for a total of 181 references. The flow chart in Figure 1 reports the process leading to the identification of 45 papers included for qualitative synthesis. Three papers were meta-analyses, 17 papers reported the results of questionnaire-based studies in non-commercial (n=6) and commercial drivers (n=11), and 25 papers reported the results of sleep study-based investigations.

Current knowledge and limitations of existing practice

Obstructive sleep apnoea (OSA) has been reported for several decades to be associated with an increased risk of MVA (12) and this risk has been quantified in various studies to range between two and seven times the risk of control populations (13). However, the comparison of reports regarding accident risk in OSA is complicated by methodological differences with some studies comparing OSA drivers to a control group, while other reports compare with the general population. Some studies also adjusted for possible confounding factors such as driving frequency and distances, visual difficulties, alcohol consumption and obesity. The methodology of accident recording also differs between reports with some providing a prospective assessment of a population sample, whereas others evaluate specific driving accidents presenting to the Emergency Department.

Table 3, e-supplement summarises the results of questionnaire-based studies in drivers, separately for non-commercial and commercial drivers. Most studies were cross-sectional association studies, based on self-administered questionnaires (mainly Epworth or Berlin) and a history of previous MVA, in addition to anthropometric measurements. In non-commercial drivers, sleepiness and OSA risk were associated with increased risk of MVA in some reports (4, 14, 15), but not in others (16-18). MVA were self-reported, with no objective verification. In elderly subjects, the risk of OSA was not associated with MVA (18). In commercial drivers, the response rates were low but self-reported sleepiness was associated with increased risk of MVA (19-21). The estimated OSA risk was associated with sleepiness in some (22, 23), but not all studies (21, 24, 25). Only some studies reported an association of OSA risk or sleep disorders and MVA rate (23, 25-27), whereas other studies were negative (28, 29).

Table 4, e-supplement summarizes the results of systematic reviews and meta-analyses, as well as sleep study-based investigations in general population, commercial drivers, and patients with OSA. An increased risk of MVA was reported in untreated OSA, with an OR range between 2 and 3. Dose-effect relationships were reported between OSA severity and risk of MVA in the general population (30-33), but short sleep duration and/or self-reported sleepiness also played a role (30, 34). According to other studies, sleepiness, but not PSG measures, was associated with occurrence of MVA (34, 35). In these studies, documented OSA was associated with a high OR for MVA (range 3.0-8.5). In professional drivers, the same trend was observed (27, 36-38), with some studies underlining a major role for sleep deprivation (39), or sleepiness (40), or nocturnal hypoxaemia (36). Conversely, Stevenson et al. found no difference in MVA occurrence between heavy-vehicle drivers with and without moderate or severe OSA (41). In sleep clinic samples, the association between OSA and MVA was confirmed, but some studies found no dose-effect relationship between OSA severity and MVA risk (42-46). Some studies reported that severe OSA patients were especially at risk (43, 47-49) and another study found that young male OSA patients showed a high risk of MVA (47).

The variability in results is partly accounted for by the difficulty in obtaining reliable information on MVA and sleepiness, especially in commercial drivers, the retrospective nature of investigations, and possibly the different phenotypes of OSA, since about half of

OSA patients do not report excessive daytime sleepiness. Moreover, most data regard male drivers, while few studies assessed MVA risk in female or elderly drivers.

Statement

- OSA increases the risk of MVA. (B)
- A high percentage of professional drivers have a high suspicion for OSA. (C)

Questionnaires have low sensitivity and low specificity for the detection of sleepiness and accident risk in professional drivers. (C)

Recommendation for research

There is a strong need for good quality studies on this topic to clarify the relative importance of EDS, SDB severity and other OSA-related variables in quantifying MVA risk.

Pathophysiology and Predictors of Excessive Daytime Sleepiness (EDS) in OSA

Search Criteria

Sleepiness is a major factor contributing to occurrence of MVAs. The search criteria for predictors of sleepiness in OSA and obese patients are reported in the e-supplement. The final selection for analysis included 42 papers for sleepiness in OSA (Table 5, e-supplement) and 12 papers for sleepiness in obesity (Table 6, e-supplement).

Current knowledge and limitations of existing practice

Table 5, e-supplement summarises the studies on determinants of EDS in OSA patients. Some studies examined EDS in OSA by PSG+MSLT (50-59) in order to identify variables potentially predictive of objective EDS. Results were variable, but a high sleep efficiency and long sleep duration in sleepy patients were found in three studies (53, 54, 57). A role for nocturnal hypoxaemia in predicting EDS was suggested by 6 studies (50, 51, 54-57). Recently, Li et al. (59) reported that mean sleep latency was positively associated with interleukin-6 level, and

negatively associated with cortisol levels. In the same series of patients, results of psychomotor vigilance testing (PVT) correlated with the ESS score but not with results of MSLT (58).

Studies using the ESS questionnaire to assess subjective EDS were more consistent with regard to the severity of nocturnal hypoxaemia as a predictor of EDS (50, 51, 54-57, 60-69) or poor performance at cognitive tests (70). Zamagni and co-authors (51) reported that subjective EDS was associated with markers of respiratory effort during apnoeas. Sleep fragmentation was associated with ESS scores in some (53, 56, 57, 60, 61, 71) but not in other studies (4, 54, 63). Large cross-sectional population studies using more liberal definitions of EDS (72-74) reported no association between EDS and sleep variables, but an association with several comorbidities, similar to the study by Koutsourelakis and co-workers in OSA patients (75). A strong association between subjective EDS and depression in OSA has been reported by several studies (66, 74-78). No difference was reported in EDS between men and women with OSA (79). One study comparing normotensive and hypertensive subjects reported higher AHI and ODI in hypertensives, but less EDS in hypertensive compared to normotensive patients with moderate-severe OSA (80). Excessive daytime sleepiness was associated with insulin resistance or Metabolic Syndrome in some (55, 81) but not in other studies (65). Other metabolic changes in OSA, i.e. higher hypocretin-1 and lower ghrelin, were reported in patients with EDS compared to patients without EDS (82). A genetic marker of EDS in OSA has been recently identified in the AMOT gene and the related P130 protein, but these findings need confirmation in larger datasets (83).

Depression and obesity predicted EDS better than AHI in a large cohort of OSA patients at diagnosis, whereas no relationship was found between EDS and AHI in non-REM or REM sleep (84). In subjects with mild OSA from the general Korean population, slight differences were reported between OSA and non-OSA subjects, but no predictor of EDS could be identified (85).

Two studies (56, 86) reported combined analysis of subjective and objective EDS. Sun and co-workers confirmed the role of both hypoxaemia and sleep fragmentation as determinants of EDS. The study by Prasad and co-workers in OSA patients reported an independent

association of EDS and African-American race, inflammatory markers, and short sleep duration.

Other studies (summarised in **Table 6, e-supplement**) analysed the association of obesity and EDS. A meta-analysis found that EDS decreased after weight loss without evident relationship with changes in AHI (87). In patients undergoing bariatric surgery, EDS was related more to metabolic variables and depression than to AHI (88, 89) or no relationship was found between AHI and EDS (90). Non-surgical weight loss in obese patients was associated with decreased ESS scores and improved insulin sensitivity (91).

Case-control studies reported 35% to 57% prevalence of EDS in obese patients without OSA (92, 93), but no relationship between ESS scores and anthropometric or sleep variables (93), confirming previous findings from the same group (94). A longitudinal study in the general population reported changes in EDS associated with weight gain or loss, and a significant influence of comorbidities and depression over a follow-up of 7.5 years (95). Analysis of 5-year follow-up data from the Sleep Heart Health Study confirmed the role of weight gain in increasing EDS, but only in women, with OSA severity explaining about 20% of the relationship (87). In obese OSA patients, nocturnal hypoxaemia predicted EDS (96) or level of alertness at MWT (97). In a sample with heterogeneous sleep disorders, the presence of obesity but not absolute BMI values predicted EDS (98).

Statements

- No major differences are evident between predictors of subjective and objective sleepiness, although most data relate to subjective sleepiness. (C)
- AHI is not useful to predict EDS in OSA, whereas most studies suggest an association of nocturnal hypoxaemia with EDS. (C)
- Obesity is a risk factor for EDS that is only partly mediated by associated OSA. (C)
- Depression, metabolic variables, comorbidities and genetic background all play a role in EDS pathogenesis. (C)

Suggestions for designs for future studies / Recommendation for research

The variables: obesity, severity of nocturnal hypoxaemia, comorbidities, and depression should be considered in future studies on sleepiness in OSA patients.

Role of Questionnaires as screening tools for OSA in Drivers

Search criteria

Database individually searched: PubMed. Keyword combinations: "Sleep apnoea" AND "screening"; "Sleep apnoea" AND "Epworth Sleepiness Scale"; "Sleep apnoea" AND "Berlin Questionnaire"; "Sleep apnoea" AND "STOP-Bang"; "Sleep apnoea" AND "drivers"; "Sleep apnoea" AND "driving". Only papers that validated the questionnaires versus P(S)G were considered. We excluded papers on OSA screening in surgical patients or pregnancy. **Table 7, e-supplement r**eports a summary of meta-analyses (n=7). **Figure 2** illustrates sensitivity and specificity of screening questionnaires for OSA defined as AHI>15 in samples from the general population, clinic population, sleep clinic, and drivers (n=16 studies).

Current knowledge and limitations of existing practice

Risk stratification in high risk populations and triage of patients in the context of driving is highly desirable, as the diagnostic capacity of sleep centres is limited and waiting lists are growing (99). Relevant clinical information should be obtained by a detailed medical history and careful clinical examination of subjects with suspected SDB. However, it may be hard to produce objective, reproducible findings, due to observer and reporter bias. Therefore, several screening questionnaires which incorporate risk factors, clinical symptoms and physical examination parameters have been developed to facilitate the diagnosis of OSA (100-104). ESS, Berlin Questionnaire, STOP and STOP-Bang are most studied in this context. These tools can be considered as an inexpensive approach that is easy to administer with minimal discomfort. However, discriminant ability of the test for OSA is a concern and is of utmost importance.

In the general population, an extreme variation can be found in the sensitivities and specificities for all established questionnaires [ESS sensitivity 18-85%, specificity 22-98%; Berlin Questionnaire sensitivity 40-97%, specificity 6-100%; STOP sensitivity 33-98%, specificity 10-95%; STOP-Bang sensitivity 0-100%, specificity 0-100%], even taking into

account the cut-off thresholds for OSA (AHI≥5, AHI≥15, AHI≥30) (**Table 7, e-supplement**). A similar pattern can be visually appreciated in **Figure 2** reporting the results of single studies in different populations. Sensitivity was highest in sleep clinic samples for all questionnaires, while the ESS showed an overall poor predictive value. In clinical population samples (i.e., patients admitted or followed for disease other than OSA), on average the BQ showed a higher sensitivity compared to the STOP-Bang. Clearly, the data indicate that questionnaires do not reliably rule in or rule out the presence of OSA.

Statements

- Most studies on screening tools are observational (large cohorts or case series), and show a poor sensitivity or specificity, resulting in an unacceptable high number of missed cases (false negative) and false positive ones. (C)
- The range in reported sensitivities and specificities, even in the same high-risk population and for similar thresholds of AHI, is huge. (C)
- The most simple questionnaire for sleepiness, the ESS, is not able to discriminate patients at risk for sleep apnoea. (C)
- In a setting of professional drivers and high-risk populations, in addition to a skilled history and examination, it is the authors´ current practice to proceed straight to an appropriate sleep study and perform objective physiological monitoring.

Future research priorities

- Evaluation and validation of new questionnaires in the complete range of OSA severity, and in different target groups (general population, drivers, high risk groups).
- Combination of screening questionnaires with nocturnal pulse oximetry.
- Development of new questionnaires, with higher sensitivities and specificities, and assessment at which AHI threshold and questionnaire score these questionnaires perform best.

Evaluation of Sleepiness

Current knowledge and limitations of existing practice

The objective assessment to identify subjects at high risk for driving accidents, in order to comply with current EU regulations, represents a major problem. While most research on OSA concentrates on sleepiness, driving fitness may relate more to vigilance, i.e. the ability of an individual to maintain focus of attention and to remain alert to stimuli over prolonged periods of time (105). Vigilance decrement is not simply the result of being exposed to repetitive or boring tasks; recent research has shown that vigilance tasks are capacity-draining, resource demanding and associated with considerable workload and stress (105). The entire spectrum of sleepiness from complete wakefulness to overt sleep is one of the factors affecting vigilance.

However, vigilance is a complex phenomenon; sleep deprivation and vigilance decrement are unlikely to be functionally equivalent. Over the last 3 decades, attempts have been made to develop objective and subjective tests for assessing the effects of sleep deprivation on vigilant attention, then extrapolating the results to driving ability (106). A description of the most frequently studied tests reported in the literature in relation to sleep disorders is available in the e-supplement.

Published studies prior to 2006 on tests of vigilance for driving are limited by poor methodology, variable patient populations, insufficient information about sleep debt, caffeine/nicotine/drug intake and circadian fluctuation in vigilance/attention which might affect performance on the day. Furthermore, they are generally not controlled for factors such as age, sex and degree of driving experience. From epidemiological as well as larger scale surveys in a variety of populations, it remains reasonably clear that MVA rates are likely to be higher in those who drive further after occurrence of sleepiness, have more sleep debt and who also have a sleep disorder (most commonly OSA) disrupting sleep quality (107-109).

Which type of test should be used?

Several tests are available to assess objective vigilance and sleepiness, respectively (see E-supplement for details):

a) Psychomotor vigilance test (PVT) - vigilance
b) Divided Attention Driving Task (DADT) - vigilance
c) Sustained Attention to Response Task (SART) - vigilance
d) Oxford Sleep Resistance Test (OSLER) - vigilance
e) Multiple Sleep Latency Test (MSLT) - sleepiness

f) Maintenance of Wakefulness Test (MWT) - vigilance

Most of the available studies involve the effects of sleep deprivation or other diseases with hypersomnia, without a specific focus on driving. For the purpose of this report, MWT is often used in the evaluation of fitness to drive, and many studies regard the interrelationships between different tests and/or sleepiness questionnaires. Several studies analysed the results of MSLT and MWT relative to results of driving simulation, as described in the following section. Similarly, divided attention is usually tested during driving simulation (DADT) and is also reported in the following section.

PVT

PVT is a 10-min test easy to perform in the clinical setting. Sanwoo and coworkers (110) compared single administration of several tests at different times of the day, and reported that results of PVT showed good agreement between tests for both reaction time and number of lapses. Cori and coworkers recently reported that reaction times at PVT were similar in OSA patients and controls, but OSA patients experienced a higher number of lapses, and performed poorly in neurocognitive tests (111). Importantly, PVT could be used in the occupational assessment of professional drivers (112). Despite being used extensively in numerous studies over the last 3 decades in assessing vigilance as related to sleep deprivation in OSA, no absolute parameters have been derived which can be utilised in a predictive manner to assess ability to drive safely.

SART

Only one study on 12 patients with untreated OSA has used the SART and no correlation was found between SART performance and the results of MSLT (113). To date, there is a lack of normative data and there are large variations in testing depending on circadian influence, age and other variables (113).

OSLER

As with the MWT, the original test comprised four 40-min sessions (114), but other investigators have developed shorter versions with 1, 2 (111), or 3 sessions, or with 20-min sessions, or combined the test with additional testing protocols such as the multiple

unprepared reaction time tests (MURT) (106, 115). A modified version of OSLER test revealed associations between poor performance at the test and previous occurrence of MVA (116). The OSLER test appears to be a sensitive test for identifying sleepiness in OSA patients and also fluctuations in vigilance throughout the day. However, normative data are not available.

Tests assessing sleepiness

Multiple Sleep Latency Test (MSLT)

The MSLT is considered as the 'gold standard' for assessing sleep propensity and is used most notably in the diagnosis of disorders of central hypersomnolence, such as narcolepsy and idiopathic hypersomnolence (117). The test is not designed to measure sleepiness routinely as it is time-consuming and extremely labour-intensive, relying on a standardised approach and scoring sleep in real time undertaken by highly trained technical staff (117). Additionally, it is not available in all centres that care for patients with OSA. However, any patient with a mean sleep latency of <8 minutes is considered to be pathologically sleepy and this correlates with increased risk of driving accidents (106).

Maintenance of Wakefulness Test (MWT)

Several studies have shown that mean sleep latency on the MWT correlates with ability to perform using a driving simulator in patients with untreated OSA (118-120). Patients with pathological MWT sleep latency scores (0-19 min) displayed significantly more interline crossings and standard deviation from the centre of the road (118, 121). Subjects and controls least likely to incur errors had a mean sleep latency of >34 minutes (118, 121).

Questionnaires and driving

As discussed earlier, a number of sleep questionnaires have been designed and used to assess excessive daytime sleepiness in a clinical setting, including the ESS (6), the pictorial ESS (122) and the Karolinska Sleepiness Scale (KSS)(123). However, these tools are subjective and do not consistently correlate with objective measures of sleepiness (124). They were also not designed to specifically assess the risk of driving impairment in OSA. One study has shown that an ESS score ≥ 13/24 appears to predict objective sleepiness, which is higher than what

has typically been used in clinical practice (≥11/24) (125). However, there is no correlation with driving safety.

Is there a relationship between real life driving performance and performance on tests of vigilance and tests measuring sleepiness?

Driving is a complex task. Driving requires the integration of psychomotor, cognitive, motor and decision-making skills, visual-spatial abilities, divided attention, and behavioural and emotional control. Sleepiness will affect a number of these factors to varying degrees which in turn are determined by individual levels of resilience and resistance to impairment as well as age, gender and baseline neurocognitive function. Many of the tests used to assess driving ability in the context of OSA are unidimensional, do not have established normative data in the overall population with respect to sleepiness and are unable to control for factors noted above. Although many are relatively easy to deploy in clinical practice, they are likely to have value only for intra-individual changes e.g. before and after treatment. Furthermore, testing fitness to drive in terms of sleepiness and vigilance may not be necessary in all patients diagnosed with OSAS, possibly only a small subset (125, 126). Taking the above caveats into consideration, the following statements can be made:

Statements:

- The DADT, PVT and OSLER are currently used as objective screening tools for impaired vigilance due to excessive daytime sleepiness in OSA before and after treatment. Results would be specific to the individual only. (C)
- There is reasonable data to correlate performance on the MWT (in respect of mean sleep latency) to driving impairment in a variety of sleep disorders, including OSA.
- A mean sleep latency of 34-40 minutes using the MWT – 40-minute protocol reflects good alertness across a day. However, results of MWT do not consider other determinants of driving ability. (C)

Recommendations for future research

- The MWT should be correlated with driving outcomes in real-life situations and in larger groups of patients with OSA as well as controls.
- There is a need to identify cost-effective and reliable ways of objectively assessing driving ability. Sleep debt, circadian influences, driving proficiency, neurocognitive function, drug intake, emotional stability, age and gender should be incorporated into algorithms to establish normative data across a diverse range of populations.

Driving Simulators in the Evaluation of Fitness to Drive

Search Criteria

A PubMed search by using the following terms: "driving simulator"[All Fields] AND "sleep apnea"[All Fields] and papers were selected as depicted in **Figure 3.** Papers were selected and examined according to the subjects in which the assessment was obtained, i.e., normal subjects (n=5 studies), and untreated OSA patients (n=32) (**Table 8, e-supplement**). **Table 9, e-supplement** summarises 12 studies on driving performance before and after CPAP treatment.

Current status and limitations of existing clinical practice

There is significant heterogeneity among driving simulators, ranging from those based on a personal computer, with very simple graphics, using a gaming steering wheel and vehicle controls through to fully immersive simulators, involving full-size real cars with full visual, motion and audible feedback, which closely replicate the real driving experience. Some studies have evaluated different components of driving in separate neuropsychiatric tests rather than integrated into a simulator or in addition to a simulator (28, 45, 127).

A hierarchy can be considered, from the “steer clear” test, to divided attention driving simulators (DASS), to PC-based simulators with realistic graphics and vehicle controls, to highly sophisticated simulator or real life driving (description available in **e-supplement**).

Less realistic simulators are associated with more events, both in patients and normal subjects. For example, in one study using a DASS (119), while patients had more off road events than general subjects, both still had unacceptably high instances (90±71 versus 40±36

per hour) which is not reflective of real world normal driving. This was also seen in other studies. By contrast the number of events during longer drives on more realistic simulators is much more consistent with real life driving. Ghosh et al (128) showed that over 50% of patients with a moderate-severe OSAS could complete approximately one hour of motorway driving without deviating out of the assigned lane, crashing etc. When driving performance is evaluated through quantitative performance measures, simulated driving is generally worse with higher absolute values compared to real road test driving (129). However the more realistic the driving experience the greater the cost, which is not realistic for an everyday clinical test. Real life road driving is not practical nor ethical (it would not be appropriate to test someone in whom there was a high likelihood of an accident).

The most commonly evaluated endpoints on the simulator include: crashes, near misses, drifting out of lane (inappropriate line crossings), how well the individual maintains their position on the road (tracking error, standard deviation of lane position or SDLP, lane position in centimetres) reaction time and speed adjustment. SDLP most consistently correlates with sleepiness and performance on the simulator (128, 130, 131).

Patients with OSA perform differently to normal subjects on a driving simulator

That patients with OSA perform worse than normal subjects on driving simulators is a consistent finding (28, 45, 119, 121, 132-147). This is true for crashes and drifting out of lane/line crossings, but also continuously measured variables, such as SDLP, or equivalent. Furthermore, performance on simulators is worse in situations in which real driving performance would be expected to deteriorate, e.g. after alcohol or sleep deprivation (140, 144, 148, 149) and improves following treatment of the sleep-disordered breathing (35, 127, 134, 141, 144, 149-153). Simulated driving is worse in sleepy patients (118, 120, 121, 154-156) consistently across the whole range of simulator types. Several studies (128, 130, 152) have shown that females perform worse than males on simulators.

Relationship between real life driving performance and performance on a driving simulator

Most of the studies reviewed either used a driving simulator to help understand mechanisms by which OSA might compromise safe driving, as a comparator with sleepiness as measured by MSLT or MWT, or as an end point to indicate effective treatment. Few studies compared

simulated with real-life driving. Relationships, albeit weak, were found with self-reported sleepiness in general (ESS), accidents, episodes of drowsing or sleepiness at the wheel (129, 130, 157-159). These relationships were seen with steer clear (130, 157), DASS (158) and more sophisticated PC based simulators (129, 159), but some studies were negative (45). Studies involving the most realistic simulators involved too few subjects for meaningful comparison with real life events.

Can driving simulators be used to help in advising patients with OSA /OSAS as to whether they are safe to drive or not?

The driving performance of sleepy individuals in a driving simulator is partially related to their real-road test driving performance. However, based on the current evidence, simulated driving performance is not able to reliably predict real-life near misses or accidents on an individual level. When comparing simulated and real driving, the strongest association was found for driving simulation near-misses or accidents with real-life rates of near-misses or accidents, followed by the number of inappropriate line crossings and the SDLP. It is not surprising that the simulator does not accurately predict accident risk; the individual who has a crash in a real car due to sleepiness will very likely have been driving that same car on many previous occasions without incident. Accidents are also caused by other drivers, and due to factors other than driver sleepiness, such as mechanical failure.

Statements

- Driving simulators, depending on their degree of sophistication, variably replicate real driving. (C)
- Poor performance on a simulator, across the whole range of simulator types, is associated with subjective and objective sleepiness, due to a variety of causes (C)
- Poor performance on a driving simulator does not predict accidents or performance during real driving, but may set an alert about whether that individual is safe to drive (C)
- It remains open whether a more realistic driving simulator has more reliable prognostic power compared to the less realistic varieties. (C)
- Simulators, used in the current way, may not be suitable for assessing fitness to drive in females. (C)

- Simulators do have a role in the assessment of whether a patient with OSAS is safe to drive but this determination requires a multi-faceted approach by an experienced clinician. (C)

Priorities for future research

- standardisation of simulator outcomes,
    - determining which of the many outputs available from a simulator are the best predictors of real life events,
    - optimal length of test,
- a consistent definition of accidents and near misses and whether attributable to driver fatigue, (although less subject to recall bias and dishonesty, official records are not widely available and will not pick up near misses etc).
- Role of simulators in females.

Effectiveness of continuous positive airway pressure (CPAP) treatment in obstructive sleep apnoea (OSA) among commercial and non-commercial motor vehicle drivers

Search Criteria

A combined computerised and manual systematic search of medical literature was performed and the respective publications were retrieved from electronic search engines. We used keywords “CPAP” and “DRIVERS”. Then words “accidents,” “collisions,” “quality of life”, “cognitive impairment”, “vigilance”, “fatigue”, “drowsiness” and “depression” were added. Main inclusion criteria were: articles published in English; data on human subjects; no reviews, guidelines or case reports; at least three subjects included; and cardiorespiratory monitoring or polysomnography (PSG) available. The search strategies for each chapter are presented in the online supplement. Data were independently extracted and analysed by two authors and final decision was reached by consensus. The selection process is indicated in

Figure 4. From 73 articles considered relevant, 34 were included (**Table 11, e-supplement**) and a further meta-analysis of CPAP efficacy in OSA is given in Table 10, e-supplement.

Current status and limitations of existing clinical practice

1. Impact of CPAP treatment on motor vehicle crash risk among drivers with OSA.

CPAP is the treatment of choice for OSA. However, the question arises if it influences the increased risk of motor vehicle crashes in OSA (31, 33, 34, 44, 49, 108, 160-162) sufficiently.

Overview of the evidence

There is a lack of randomised controlled trials (RCTs). However, most observational studies (153, 163-166) indicate that CPAP reduces crash risk. Although in an early study (167) individuals who experienced non-injurious crashes appeared to gain no benefit, a recent study (166) with a longer follow-up of two years reported that the risk of near miss accidents (NMA) decreased to normal. A meta-analysis (153) also found a significant reduction in accidents. Furthermore, CPAP can annually reduce collision costs by $11.1 billion, prevent more than 500,000 collisions, and save nearly 1,000 lives (168), suggesting that CPAP is a highly efficient use of health care resources (169). A large number of PAP adherent patients studied had crash risks similar to controls, whereas non-adherent had a fivefold greater crash risk, 6 years after treatment (170). Moreover, Karimi et al. previously had shown in another large study with long-term follow up that the incidence of motor vehicle accidents (MVA) was reduced by 70% among CPAP adherent, whereas it increased by 54% among non-adherent patients (116).

Statements

- Evidence suggests that CPAP markedly reduces MVA risk among individuals with moderate-to-severe OSA. (B)
- CPAP treatment prevents most of the OSA-related motor-vehicle collisions, costs, and deaths. (B)
- Adherence of >4 h per day to CPAP is crucial for improving crash risk (B).

2. Effect of CPAP treatment on driving simulator performance in drivers with OSA.

Driving simulators enable researchers to conduct driving tests that would be too dangerous to perform in the real world or that require specific driving conditions.

Overview of the evidence

CPAP seems to improve performance in simulated driving (141, 145, 153, 171-174). Two studies, a non-randomised controlled study (152) and a prospective case series (127) indicated significant improvements following only 2 days of CPAP use. Furthermore, CPAP normalised driving simulator performance to the level of controls (163, 174). Even if it remained impaired in another small study (141), the authors suggested that some optimally treated patients may have residual deficits that could impair driving. One night without CPAP significantly worsened driving performance (175). However, in most of the above studies the number of patients was limited.

Statements

- Simulated driving performance improves significantly within 2 to 7 days of CPAP treatment (B).
- The benefits of CPAP on driving performance depend on treatment compliance (B).

3. Effect of CPAP treatment on daytime sleepiness among drivers with OSA.

Overview of the evidence

A number of studies (115, 127, 145, 152, 153, 164, 167, 173, 176-183) indicate that CPAP improves sleepiness after as little as one night of treatment. However, few of them had a randomised design (145, 173, 181, 182) . A self-rating instrument (Sleepiness Wakefulness Inability and Fatigue Test or SWIFT) was developed (178), which score was improved after PAP.

Sleepiness assessed by Multiple Sleep Latency Test (167, 171, 180, 181) and alertness by Maintenance of Wakefulness test (182, 183) both improved after CPAP.

Statements

- Subjective daytime sleepiness improves significantly after as little as one night of CPAP treatment. (B)
- Evidence suggests that objective daytime sleepiness improves with CPAP treatment. (B)

4. Effect of CPAP treatment on cognitive function among drivers with OSA.

Overview of the evidence

Limited number of studies (172, 177, 181) including only one RCT (181) evaluated cognitive function with a battery of neuropsychological tests. These tests provided subjective and objective evidence for significant improvement of cognitive function among drivers after CPAP

Statement

- Evidence suggests that cognitive function improves with CPAP treatment. (B)

5. Effect of CPAP treatment on vigilance among drivers with OSA.

Overview of the evidence

Although only five studies were included in analysis, improvements were found in the 80-min vigilance test after (180) 1 year and in the 'driving simulator' attention test, after one night of CPAP (184). More recently, CPAP resulted in objectively improved reaction times and sustained attention in OSA drivers (115). Likewise, in two RCTs studies, CPAP resulted in significant improvements in 3 (172) or all domains of FOSQ questionnaire (173).

Statement

- Evidence suggests that vigilance improves with CPAP treatment. (B)

6. Effect of CPAP treatment on quality of life and mood among drivers with OSA.

Overview of the evidence

The limited number of studies, including one RCT, showed that CPAP improves scores among OSA drivers in quality of life questionnaires (174, 179, 181). Few data are also available on CPAP on mood. Two studies, one RCT, showed that CPAP improved mood questionnaires (181, 185).

Statements

- Evidence suggests that quality of life improves with CPAP treatment. (B)
- There is only little evidence on the beneficial effects of CPAP on depressive symptoms among drivers with OSA. (B)

Priorities for future research

- Assessment of causes of residual driving simulator impairment after CPAP treatment and determination whether this is associated with persistent elevated real-life accident risk in OSA patients.
- Identification of acceptable compliance to CPAP treatment regarding driving risk.
- Evaluation of other treatment methods or combinations (surgery, oral appliances, drugs, behaviour modification) in reducing crash risk for drivers with OSA.

Discussion and conclusions

OSA is a widely accepted risk factor for MVA and effective treatment with nasal CPAP substantially reduces this increased accident risk with several reports indicating that the risk may be reduced to a level similar to the general population (186, 187). The risk of MVA has long been recognised as having extra implications for long-haul truck drivers, where drowsiness while driving is common (188), and the MVA risk is enhanced by other factors such as alcohol consumption (189) and short sleep duration (190, 191). The average increased risk of MVA has been quantified in meta-analyses and several original reports as being around 2.5 times the accident risk of control populations (13, 48, 192, 193) and a recent case control study of truck drivers reported an even higher MVA risk (OR 3.42) (194). However, not all reports indicate an increased MVA risk relating to OSA (41). It is also common for OSA patients having an accident to report a preceding history of near miss events, although the relationship with near miss MVA also differs between reports, with one large cohort study indicating a 3-

fold increase in MVA risk in OSA patients but no relationship to near miss events (195), whereas another report among truck drivers found a two-fold increase in near miss events but no relationship to MVA (20). OSA is also associated with a greater than two-fold increased risk of work accidents in general (196).

Many potential contributing factors can be considered in the increased MVA risk among OSA patients including the severity of SDB as measured by the AHI, the level of EDS typically measured by the ESS, poor sleep quality and related lifestyle factors (197), and co-morbidity (16). Reports differ on the relative importance of AHI and sleepiness as major factors in determining accident risk, which is at least partly a consequence of the poor association between subjective sleepiness and AHI (7, 8). This discrepancy likely reflects a combination of factors including the fact that many additional factors relating to lifestyle and comorbidity may influence the subjective sense of sleepiness and the relative simplicity of the ESS score itself.

The role of EDS in driving accidents has been the subject of many reports, both in OSA populations and in the context of general driving accident risk. Excessive sleepiness is reported as a contributing factor in 5-7% of MVA, and in up to 17% of accidents involving fatalities (198). A recent meta-analysis reported that sleepiness at the wheel was associated with an increased risk for MVA with an odds ratio of 2.51 (199). Another questionnaire survey of more than 35,000 drivers in France found a strong predictive value of EDS for MVA (OR 5.0 for ESS>15) and the strongest predictor of all was sleepiness at the wheel needing to stop (OR 9.48) (16). Studies using driving simulators demonstrate that the level of impaired performance in OSA drivers is similar to that seen in drivers with blood alcohol levels above the legal limit or following sleep deprivation (200). The authors' panel agrees that history of previous MVA is an important part of current clinical practice in the process of releasing or renewing driving license (Figure 5).

The comparison of AHI and EDS as risk factors for MVA has produced differing results in several studies. EDS has been reported as the principal factor contributing to MVA risk in several reports. Arita and co-authors found that EDS was the major factor in MVA in OSA patients having an MVA when compared to snorers (201). Karimi and co-authors (38) reported that ESS >15 significantly related to MVA rate whereas AHI did not. However, the

earlier report of Teran-Santos and co-authors indicated that AHI more closely related to MVA risk than ESS in 102 patients presenting to the emergency department following MVA when compared to matched control subjects (189). Furthermore, the European Sleep Apnoea Database cohort study (ESADA) also reported that OSA severity based on AHI was superior to the ESS in predicting MVA risk (202), a finding also supported by an earlier Canadian study (193). Thus, further research is needed to more clearly define the factors relating to OSA that predict MVA risk.

The problem of fitness to drive has been largely investigated in the last 30 years, but the results are far from satisfactory. Despite the large number of studies, we still lack simple instruments applicable on a large scale that could reliably indicate that a subject with OSA is fit to drive. OSA is often unrecognised and screening the population of drivers for the presence of OSA is a difficult task. Although several questionnaires have been used, their sensitivity and specificity vary according to the subjects assessed. Thus, documentation of SDB by a recording obtained during sleep remains the only reliable way to diagnose OSA. It should be the responsibility of the physician to suspect OSA and request diagnostic examination in the case of subjects renewing their driving license (Figure 6). Attention should be paid to potentially important risk factors, such as a history of previous MVAs, especially where sleepiness was a likely contributing factor, the presence of obesity, or a history of snoring. Unfortunately, this is often not the case, as shown by recent surveys of physicians (11, 203, 204). Stricter criteria for the issuing or renewal of driving licenses have been adopted in several countries for commercial drivers. A “fast track” for sleepy drivers in order to establish CPAP treatment has been recently tested (205).

Although the 2014 EU Directive for the first time considered OSA as a disease associated with driving risk, it is still unclear how OSA patients should be assessed, and which factors may predict an increased driving risk. A reduced sleep latency during the maintenance of wakefulness test (MWT) is used in some European countries to document increased sleepiness in OSA patients, but MWT requires a polysomnographic recording the night before the test, and repeated recordings during daytime, making it unsuitable to test large numbers of subjects. On the other hand, only about half of OSA patients report EDS, and clinical markers that may help identify patients at risk are lacking. Even in patients with OSA and EDS, predicting MVA risk is difficult, since the sense of responsibility of the driver plays a major

role in avoiding accidents, i.e., very sleepy patients avoid driving, or stop for a nap while driving (156).

In the case of CPAP-treated OSA, the situation is somewhat simpler, since daily use of CPAP can be documented by data download from the device, and studies have shown that CPAP treatment with good adherence effectively decreases MVA risk (187). Accordingly, documented use of CPAP for at least 4 hours for at least 70% of nights is considered as enough evidence to consider a treated CPAP patient fit to drive (Figure 6). However, residual EDS is found in about 6 to 13% of effectively CPAP-treated patients (206, 207) and its pathogenesis remains uncertain (208). Stimulating drugs such as modafinil or armodafinil to counteract EDS, and possibly MVA risk, are effective on residual sleepiness, but were withdrawn from the market due to side effects (209), while new drugs such as solriamfetol (210, 211), or pitolisant (212) may be useful in patients reporting residual EDS. Whether such drugs could be useful in OSA patients refusing CPAP treatment remains to be further studied (213).

Tests used to date have shown many difficulties as their practical application is concerned. Driving simulation, for example, could appear an easy test to perform, and experience with driving tests has accumulated over the years. However, it is not yet demonstrated that driving performance on a simulator is predictive of accidents during real driving. Nevertheless, deviations from lane, which are used as indicator of sleepiness during driving simulation, have been used to develop algorithms active in the car to improve safety on the road (214).

Despite the abundance of research on the topic, the present report indicates that significant knowledge gaps persist regarding the association of OSA with MVA. Nonetheless, several statements can be made with reasonable conviction and are indicated in Figure 7. Current research is moving in an additional direction, with identification of microsleep episodes associated with drowsiness, i.e. the intermediate state between wakefulness and established sleep. Indeed, the drowsiness preceding sleep is associated with lack of control and may be a crucial determinant of MVAs (215-217). Identification of drowsiness may be the new frontier to develop new and more applicable tests to identify risky drivers.

General recommendations for future research

- There is a strong need for good quality studies on how to best diagnose OSA and detect sleepiness in drivers.

- Research should focus on biomarkers of sleepiness (including metabolic and genetic markers) that are easily measurable and respond with detectable changes to OSA treatment.
- Gender differences should be better explored regarding variables that affect fitness to drive and assessment methods.
- Results of tests measuring vigilance and sleepiness should be correlated with driving outcomes in real-life situations.
- Further research is needed on how driving simulators can be used on a large scale, and which variables should be used to define MVA risk.
- Whether OSA-associated crash is associated with increased risk of death or injury should be evaluated.
- A clear model applicable in a standardised way in screening for OSA and identifying patients potentially at high risk for accidents is still missing.
- New technologies to prevent accidents and research on new markers, especially focusing on drowsiness-related risk, appear promising.

Legend to Figure 1.

Flow chart of selection process for epidemiological studies included in report.

Legend to Figure 2.

Sensitivity and specificity of studies evaluating various questionnaires as screening tools for obstructive sleep apnoea. References cited are:

Tan et al (218), Marti-Soler et al (219), Westlake et al (220), Avincsal et al (221), Gantner et al (222), Sert Kuniyoshi et al (223), Danzi-Soares NJ et al (224), Nerbass et al (225), Nicholl et al (226), Margallo et al (227), Faria et al (228), Pataka et al (229), Prasad et al (230), McMahon et al (231), Cowan et al (232), Kiciński et al (233), Popević et al (234).

Legend to Figure 3.

Flow chart of selection process for driving simulation studies included in report

Legend to Figure 4.

Flow chart of selection process for CPAP efficacy studies included in report

Legend to Figure 5.

The experts´ current practice of advising on Fitness to Drive according to history of previous MVA

Legend to Figure 6.

The experts´ current practice of advising on Fitness to Drive in OSA Patients

Legend to Figure 7.

The experts' summary statement regarding the assessment of driving risk in OSA patients.

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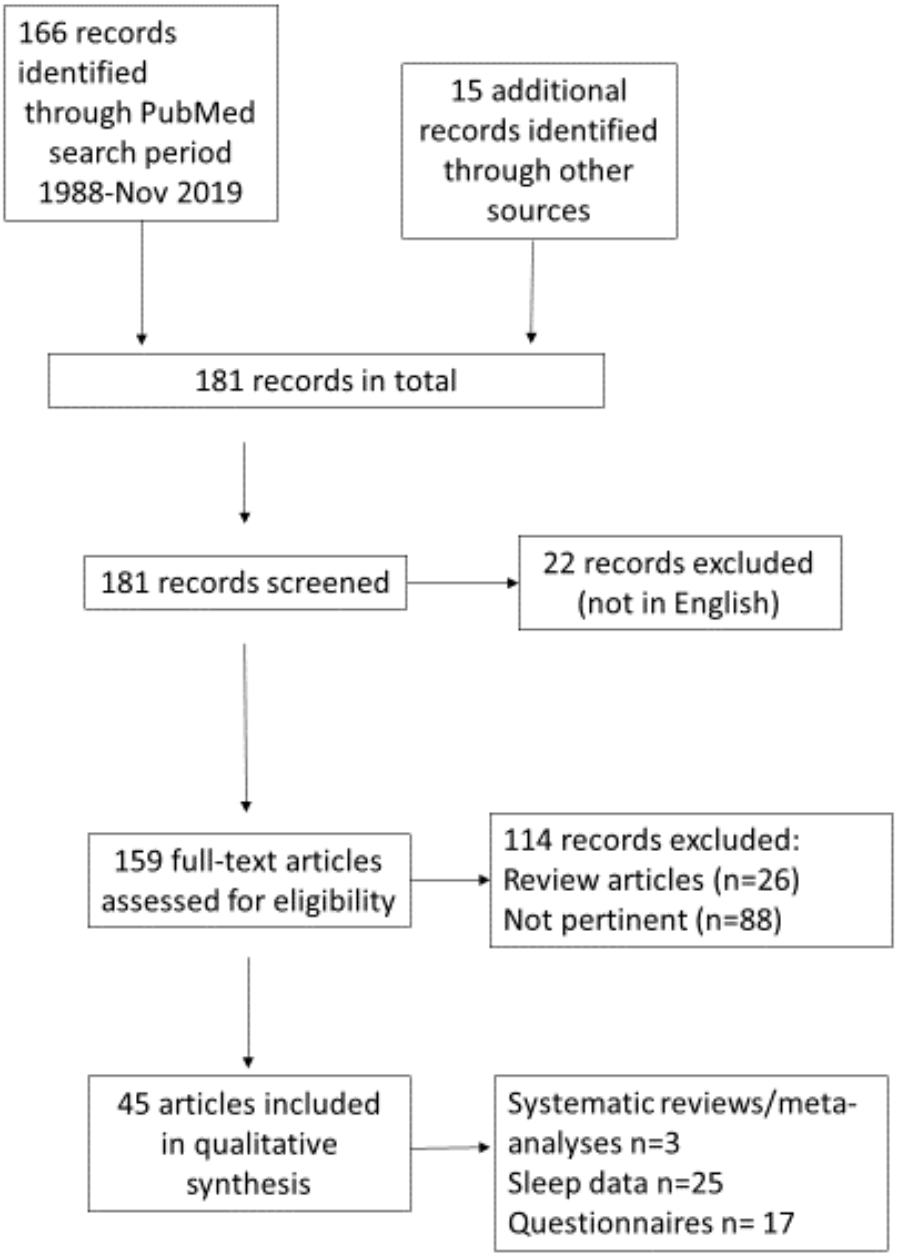
Figure 1.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Not pertinent (n=88)
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Systematic reviews/meta-analyses n=3
Sleep data n=25
Questionnaires n= 17

Figure 2a.

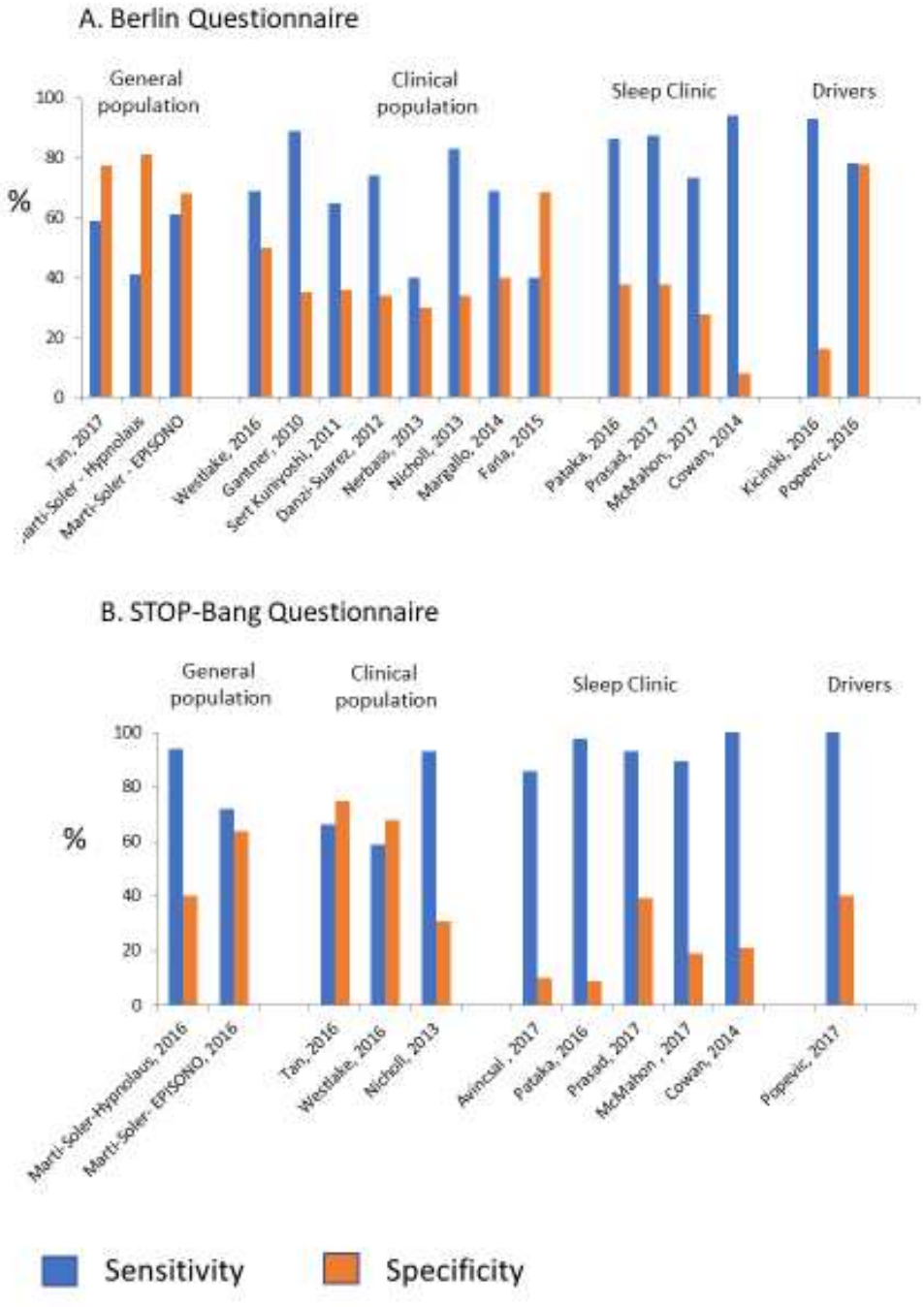

A. Berlin Questionnaire
General population
Clinical population
Sleep Clinic
Drivers
%
100
80
60
40
20
0
Tan, 2017
Marti-Soler - Hypnolaus
Marti-Soler - EPISONO
Westlake, 2016
Gantner, 2010
Sert Kuniyoshi, 2011
Danzi-Suarez, 2012
Nerbass, 2013
Nicholl, 2013
Margallo, 2014
Faria, 2015
Pataka, 2016
Prasad, 2017
McMahon, 2017
Cowan, 2014
Kicinski, 2016
Popevic, 2016
B. STOP-Bang Questionnaire
General population
Clinical population
Sleep Clinic
Drivers
%
100
80
60
40
20
0
Marti-Soler-Hypnolaus, 2016
Marti-Soler- EPISONO, 2016
Tan, 2016
Westlake, 2016
Nicholl, 2013
Avincsal , 2017
Pataka, 2016
Prasad, 2017
McMahon , 2017
Cowan, 2014
Popevic, 2017
Sensitivity
Specificity

Figure 2b.

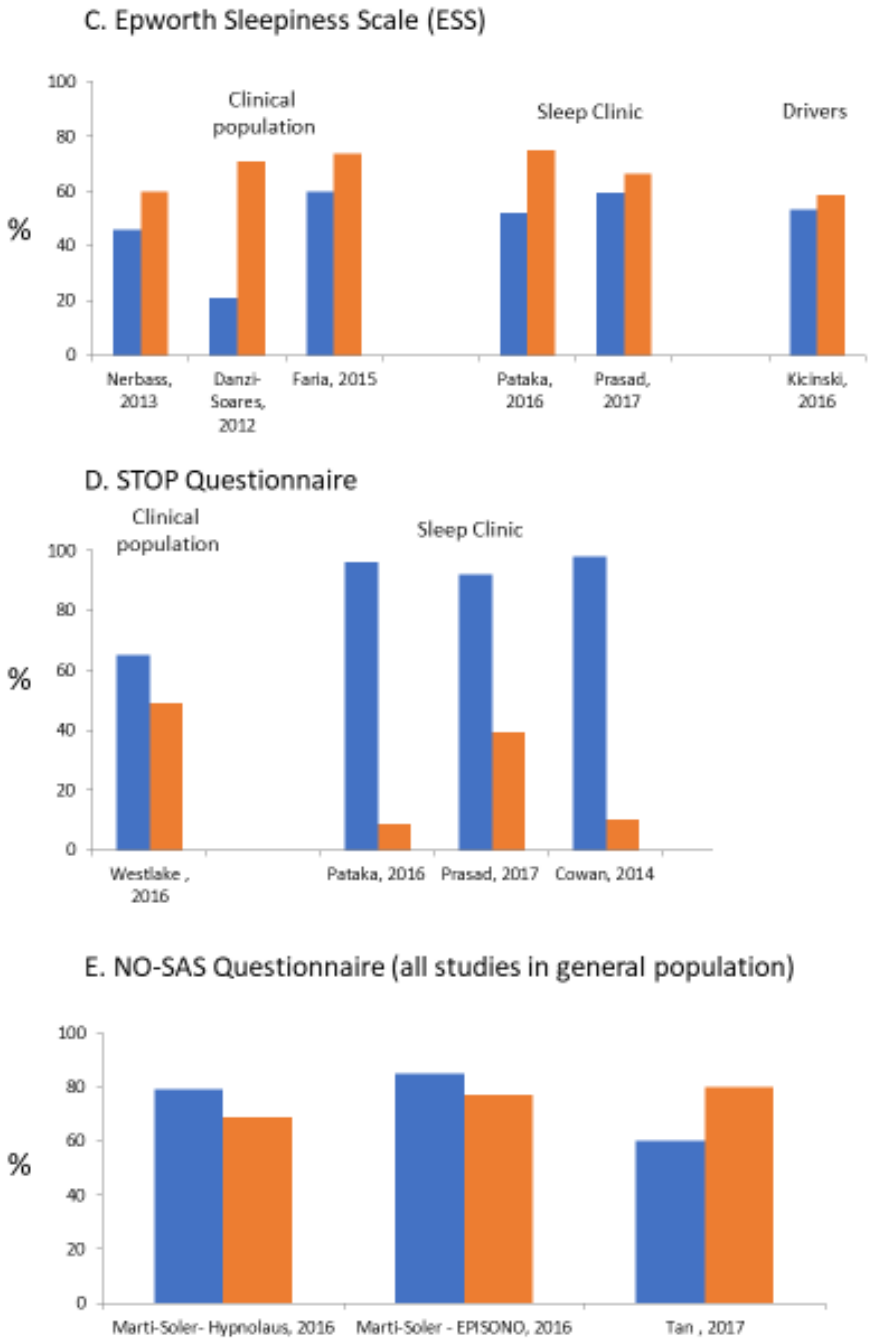
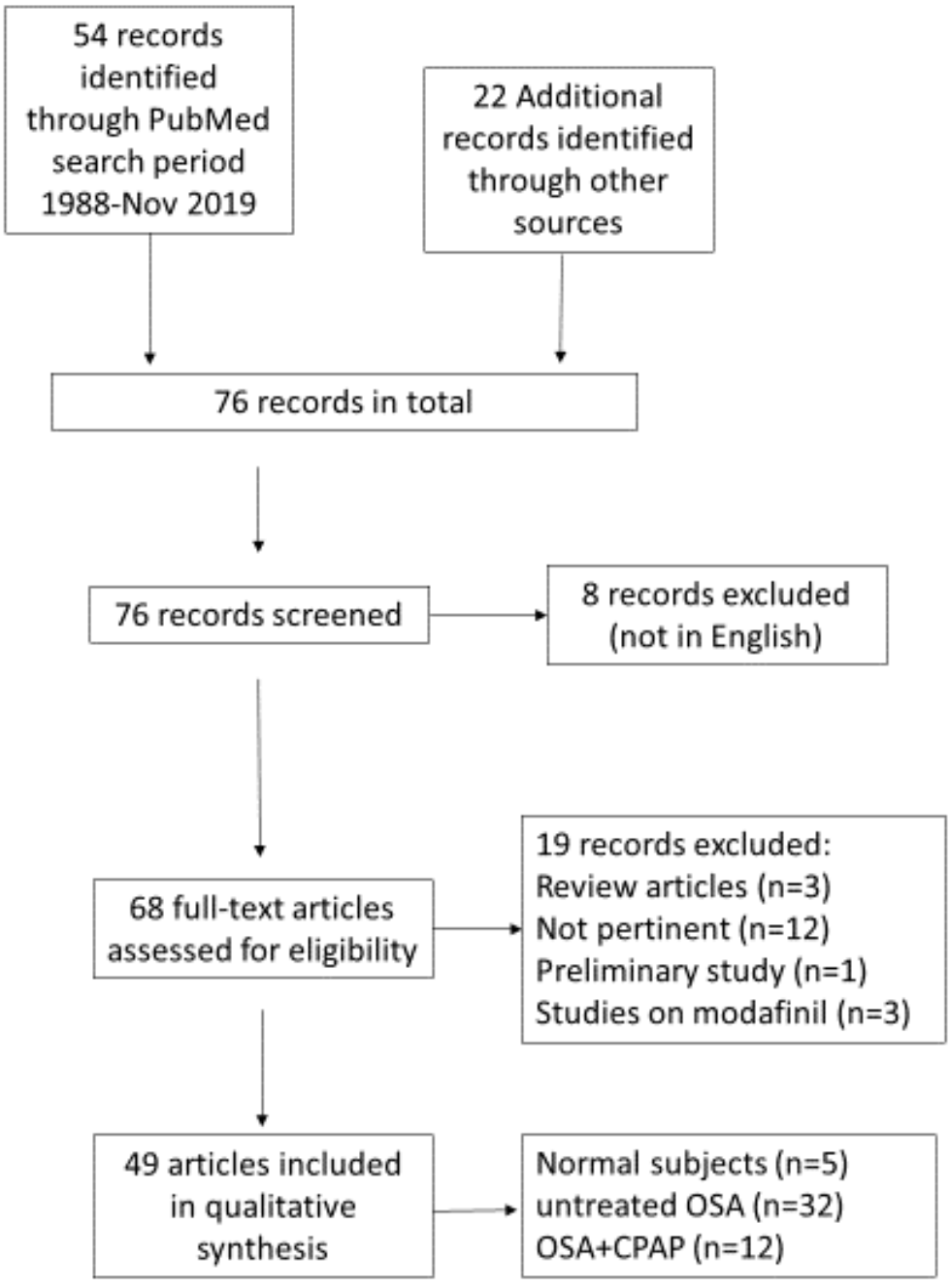

C. Epworth Sleepiness Scale (ESS)
%
100
80
60
40
20
0
Clinical population
Sleep Clinic
Drivers
Nerbass, 2013
Danzi-Soares, 2012
Faria, 2015
Pataka, 2016
Prasad, 2017
Kicinski, 2016
D. STOP Questionnaire
Clinical population
Sleep Clinic
Westlake , 2016
Pataka, 2016
Prasad, 2017
Cowan, 2014
E. NO-SAS Questionnaire (all studies in general population)
Marti-Soler- Hypnolaus, 2016
Marti-Soler - EPISONO, 2016
Tan , 2017

Figure 3.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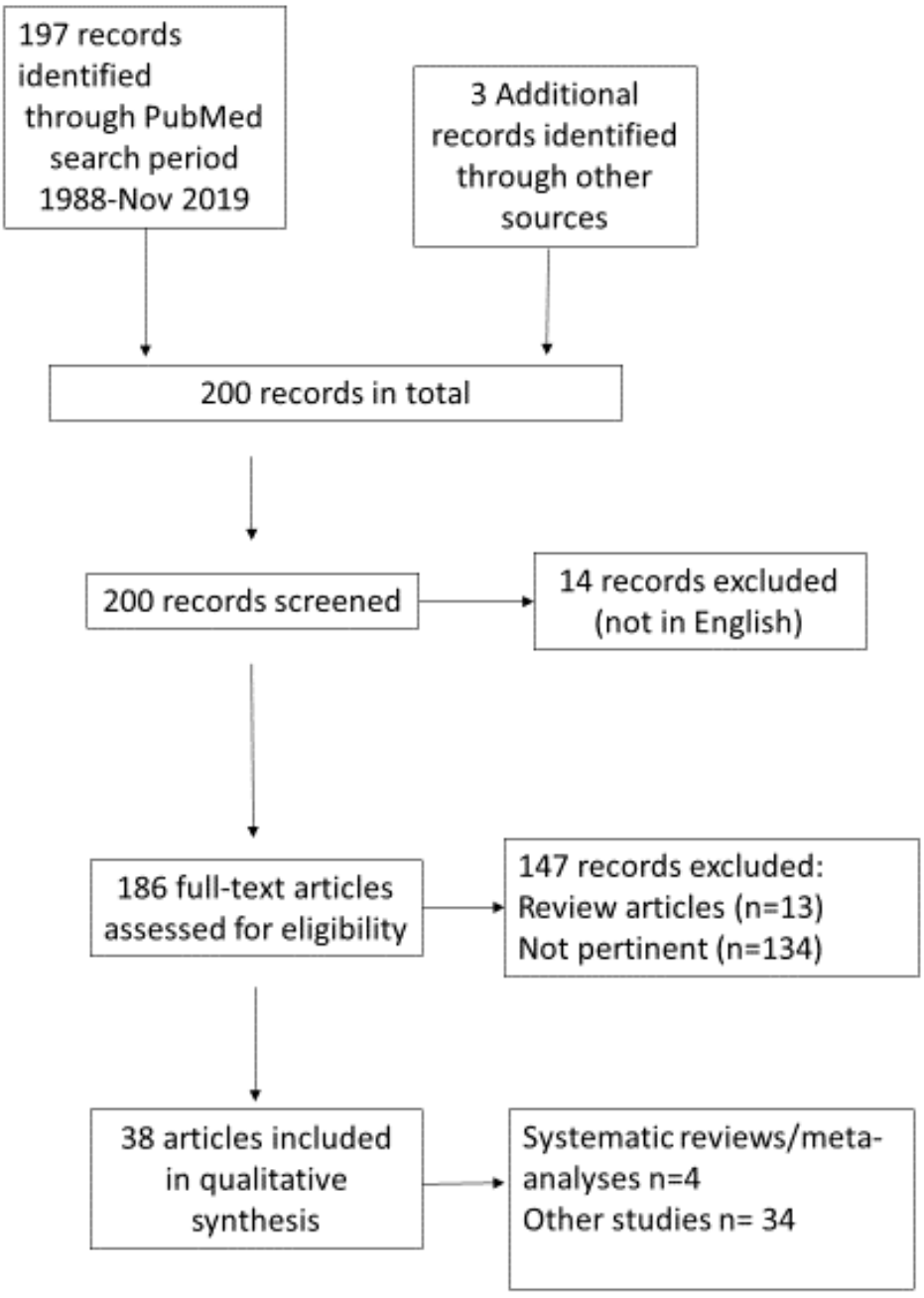
68 full-text articles assessed for eligibility
19 records excluded:
Review articles (n=3)
Not pertinent (n=12)
Preliminary study (n=1)
Studies on modafinil (n=3)
49 articles included in qualitative synthesis
Normal subjects (n=5)
untreated OSA (n=32)
OSA+CPAP (n=12)

Figure 4.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200 records in total
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14 records excluded (not in English)
186 full-text articles assessed for eligibility
147 records excluded: Review articles (n=13) Not pertinent (n=134)
38 articles included in qualitative synthesis
Systematic reviews/meta-analyses n=4
Other studies n= 34

Figure 5.

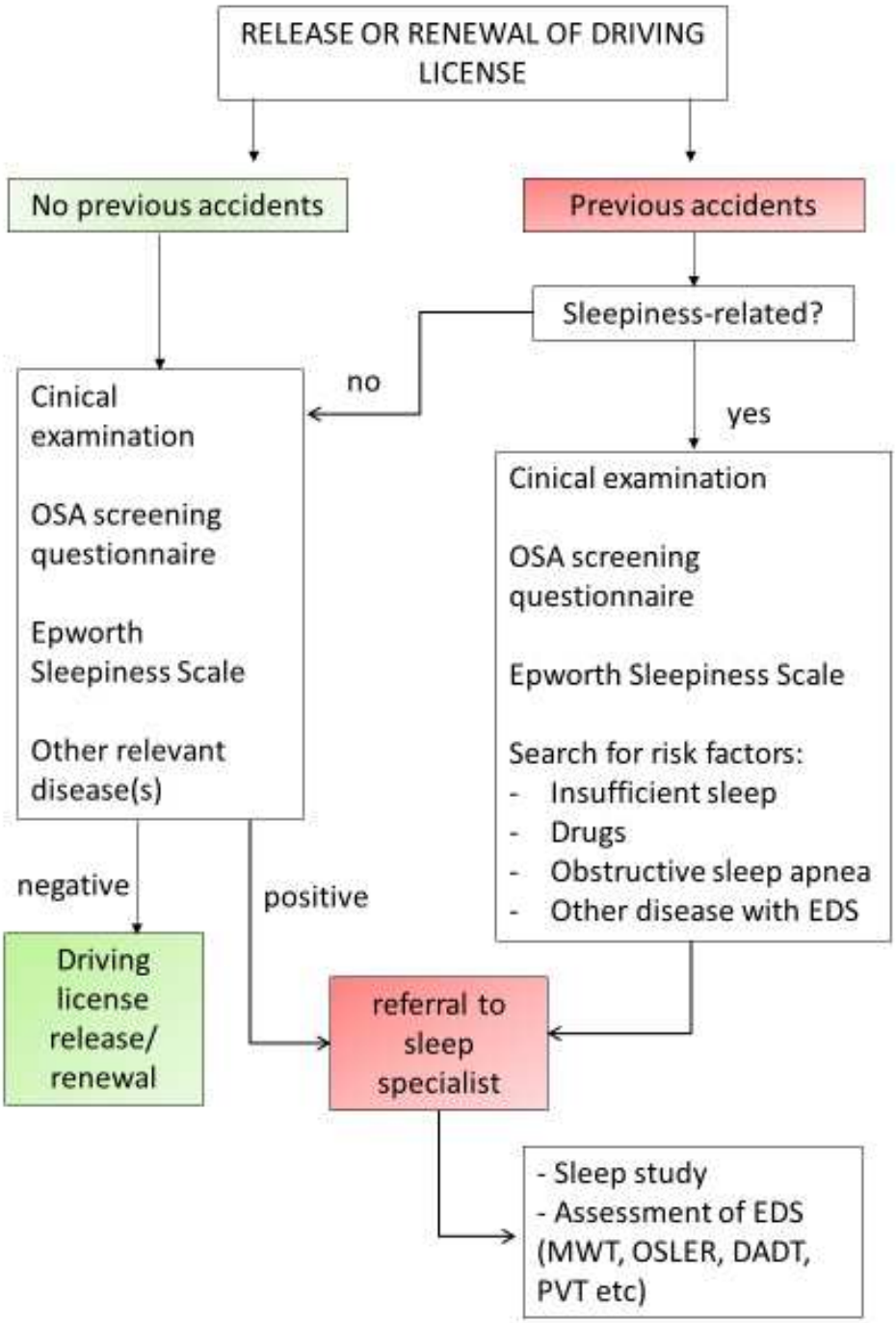

RELEASE OR RENEWAL OF DRIVING LICENSE
No previous accidents
Previous accidents
Sleepiness-related?
no
yes
Cinical examination
OSA screening questionnaire
Epworth Sleepiness Scale
Other relevant disease(s)
Cinical examination
OSA screening questionnaire
Epworth Sleepiness Scale
Search for risk factors:
- Insufficient sleep
- Drugs
- Obstructive sleep apnea
- Other disease with EDS
negative
positive
Driving license release/ renewal
referral to sleep specialist
- Sleep study
- Assessment of EDS (MWT, OSLER, DADT, PVT etc)

Figure 6.

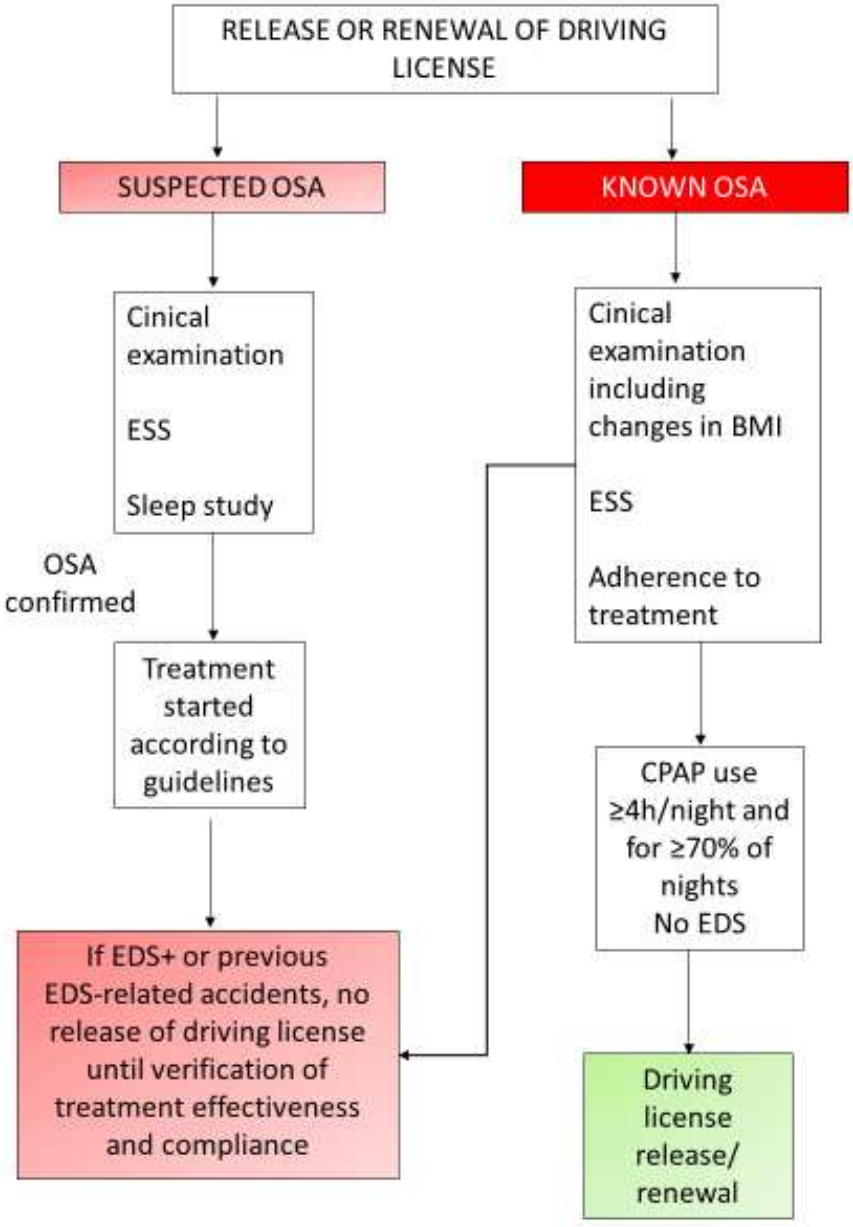
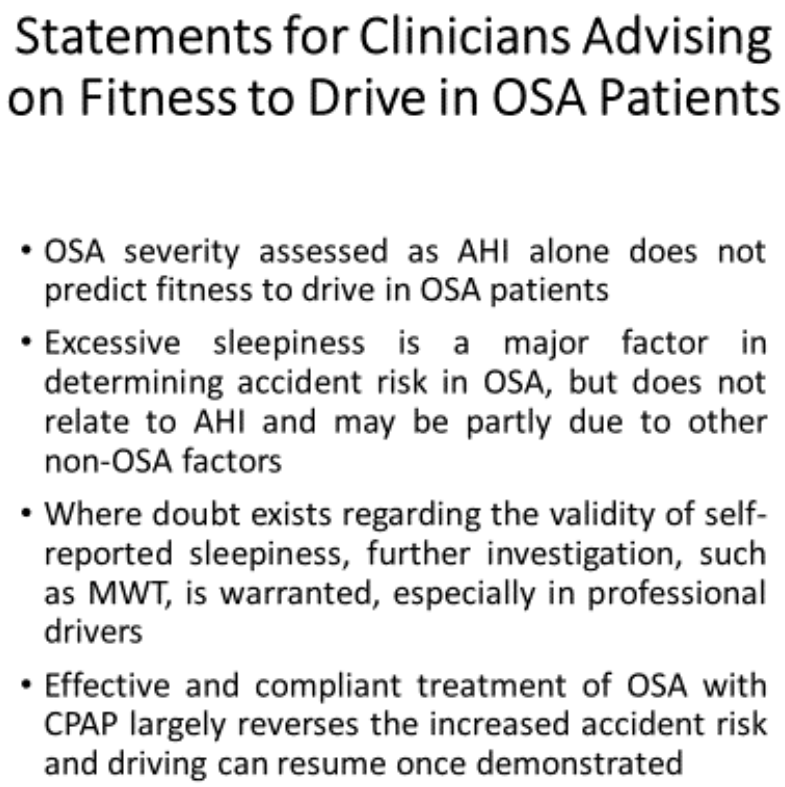

RELEASE OR RENEWAL OF DRIVING LICENSE
SUSPECTED OSA
KNOWN OSA
Cinical examination
ESS
Sleep study
OSA confirmed
Treatment started according to guidelines
Cinical examination including changes in BMI
ESS
Adherence to treatment
CPAP use ≥4h/night and for ≥70% of nights
No EDS
If EDS+ or previous EDS-related accidents, no release of driving license until verification of treatment effectiveness and compliance
Driving license release/ renewal

Figure 7.


Statements for Clinicians Advising on Fitness to Drive in OSA Patients
• OSA severity assessed as AHI alone does not predict fitness to drive in OSA patients
• Excessive sleepiness is a major factor in determining accident risk in OSA, but does not relate to AHI and may be partly due to other non-OSA factors
• Where doubt exists regarding the validity of self-reported sleepiness, further investigation, such as MWT, is warranted, especially in professional drivers
• Effective and compliant treatment of OSA with CPAP largely reverses the increased accident risk and driving can resume once demonstrated

Electronic Supplement:

Sleep Apnoea, Sleepiness and Driving Risk. ERS Task Force Report

Bonsignore MR, Randerath W, Schiza S, Verbraecken J, Elliott MW, Riha R, Barbe F, Bouloukaki I, Castrogiovanni A, Deleanu O, Goncalves M, Leger D, Marrone O, Penzel T, Ryan S, Smyth D, Steenbrugger I, Teran-Santos J, Turino C, McNicholas WT.

Predictors of sleepiness in OSA

Search terms:

Hypoxia and sleepiness, hypoxemia and sleepiness, polysomnography in OSA, polysomnography and excessive daytime sleepiness, factors of excessive daytime sleepiness in obstructive sleep apnoea, Predictor of daytime sleepiness in OSA, daytime sleepiness in OSA, sleep disruption in OSA, sleep fragmentation and excessive daytime sleepiness in obstructive sleep apnoea, sleepiness in OSA, nocturnal hypoxemia and sleepiness. Daytime sleepiness in obese, obesity and OSA, obesity and sleep relating breathing, obesity, predictors of sleepiness in obesity, sleepiness in severe obese.

Hypoxia and sleepiness and OSA: ("hypoxia"[MeSH Terms] OR "hypoxia"[All Fields]) AND ("sleep stages"[MeSH Terms] OR ("sleep"[All Fields] AND "stages"[All Fields]) OR "sleep stages"[All Fields] OR "sleepiness"[All Fields]) AND OSA[All Fields]: 112 results: after exclusion of not pertinent references (post-treatment changes, reviews, other diseases, experimental studies in animals): **5 references**

Polysomnography and sleepiness and OSA and adults ("polysomnography"[MeSH Terms] OR "polysomnography"[All Fields]) AND ("sleep stages"[MeSH Terms] OR ("sleep"[All Fields] AND "stages"[All Fields]) OR "sleep stages"[All Fields] OR "sleepiness"[All Fields]) AND OSA[All Fields] AND ("adult"[MeSH Terms] OR "adult"[All Fields]): 896 results; **37 references selected**, **total: 42 references (Table 6, e-supplement)**

Obesity and sleepiness ("obesity"[MeSH Terms] OR "obesity"[All Fields]) AND ("sleep stages"[MeSH Terms] OR ("sleep"[All Fields] AND "stages"[All Fields]) OR "sleep stages"[All Fields] OR "sleepiness"[All Fields] AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])

Results: 757 references; **34 references selected**, **12 references included (Table 6, e-supplement)**

Tests of vigilance

Psychomotor vigilance test (PVT)

The PVT is a high signal-load reaction-time test that is extremely sensitive to sleep deprivation [Lim] and has been shown to be associated with the following findings: a) an overall slowing of response, b) increased propensity to lapse for lengthy periods (<500msec) and incur errors of commission, c) the enhancement of time-on-task effect within each test d) revealing the interaction of circadian and homeostatic sleep drives [Lim]. No absolute parameters have been derived which can be utilised in a predictive manner to assess ability to drive safely.

Divided Attention Driving Task (DADT)

Divided attention can be assessed when performing two tasks simultaneously, such as a primary tracking task and a secondary visual search task. The DADT [George] measures mean tracking error at 10 minutes and 20 minutes.

Sustained Attention to Response Task (SART)

The SART is a go/no-go task which was designed to assess the ability to sustain attention, an important correlate of wakefulness [van der Heide]. The no-go target appears on a screen unpredictably and rarely. Accuracy and response speed (reaction time) are measured. In contrast to vigilance tasks which require observers to respond to critical signals and to withhold responding to neutral events, the SART features the opposite response requirements, supposedly promoting a mindless, non-thoughtful approach to the vigilance task [Dillard].

Oxford Sleep Resistance Test (OSLER)

The OSLER combines both psychomotor impairment and behavioural factors involved in maintaining wakefulness [Bennett]. As with the MWT, the original test comprised four 40-min sessions, [Sunwoo] but other researchers have developed shorter versions with 1, 2, or 3 sessions, or with 20-min sessions or combined the test with additional testing protocols such as the multiple unprepared reaction time tests (MURT) [Gupta, Alakuijala].

Tests assessing sleepiness

Multiple Sleep Latency Test (MSLT)

The MSLT has now been in use for several decades as the 'gold standard' for assessing sleep propensity and is used most notably in the diagnosis of disorders of central hypersomnolence, such as narcolepsy and idiopathic hypersomnolence [Littner]. The test is not designed to measure sleepiness routinely as it is time-consuming and extremely labour-intensive, relying on a standardised approach and scoring sleep in real time undertaken by highly trained technical staff [Littner]. Additionally, it is not available in all centres that care for patients with OSAHS.

Maintenance of Wakefulness Test (MWT)

This test assesses ability to maintain wakefulness under soporific conditions with no recourse to any stimulating activity. The test was designed as four 40-minute periods over the course of a day [Littner, Doghramji]. A shortened 20-minute protocol has shown reduced sensitivity and specificity for assessing wakefulness and should not be used if there

are questions regarding driving ability [Doghramji, Banks]. Motivation profoundly affects the Maintenance of Wakefulness test (MWT), particularly the 20-minute MWT protocol [Arzi, Shreter].

Table 1.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

1a	Systematic analysis (systematic review) of RCTs with homogenous results
1b	Particular RCT with limited dispersion
1c	Therapy, before its introduction all patients died
2a	Systematic review of cohort studies with homogenous results
2b	Particular cohort studies or RCT of lower quality
2c	"Outcomes" research; ecological studies
3a	Systematic review of case-control studies with homogenous results
3b	Particular case-control study
4	Case studies and cohort studies or case-control studies of limited quality
5	Expert opinion

RCT= Randomised controlled trial

Table 2: Grades of recommendation to use

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations of level 1 studies
C	Level 4 studies or extrapolations of level 2 or 3 studies
D	Level 5 or inconsistent studies of other levels

Table 3. Screening questionnaires on sleepiness, MVA and OSA in non-commercial (n=6) and commercial (n=11) drivers

Author	Design	EBM	Patient population and methods	Results	Comments
Non-commercial drivers					
Al-Abri et al, 2018 (1)	Cross sectional study	4	492 young adult Omani non-commercial drivers. Berlin Questionnaire (BQ) and Epworth Sleepiness Scale (ESS) along with additional questions about their sleeping habits.	124 Omanis (25.2%) reported experiencing daytime sleepiness while driving at least once per month. There was a significant association between nocturnal sleep duration of <6 hours and sleepiness while driving (*P* = 0.042). Male drivers were significantly more likely to report sleepiness while driving (*P* = 0.001). Overall, sleepiness while driving was significantly associated with ESS and BQ scores (*P* = 0.023 and <0.001, respectively).	Weaknesses: subjective information; no report on accidents
Goncalves et al, 2015 (2)	Cross sectional study	4	12,434 questionnaires (general population). ESS, STOP-Bang Questionnaire	Among men, the prevalence of falling asleep at the wheel, and of MVA due to falling asleep, increased significantly with OSA risk. A dose-response association between OSA risk and falling asleep at the wheel was found after adjustment for potential confounders: OR = 1.83 (95% CI: 1.54; 2.18) for intermediate OSA risk; and OR = 3.48 (95% CI: 2.78; 4.36) for high OSAS risk	Self-selection and recall bias ; no verification of MVA
Quera Salva et al,	Cross sectional	4	3051 drivers. ESS, Basic Nordic Sleep Questionnaire (BNSQ),	Eighty-seven (2.9%) drivers reported near-miss sleepy accidents (NMSA) during the trip; 8.5% of NMSA occurred during the past year and 2.3% reported	No verification of MVA

2014 (3)	**survey**		**and a travel questionnaire;** **data from the past 24 h and information on usual sleep schedules**	**sleepiness-related accidents in the past year. Significant risk factors for NMSA during the trip were: NMSA in the past year, nonrestorative sleep and snoring in the past 3 months, and sleepiness during the interview.**	
Philip et al, 2010 (4)	**Cohort study**	**4**	**Frequent highway drivers (n=37,648), internet based survey**	**Sleepiness significant risk factor for MVA, no increased risk with diagnosis of OSA**	**Self-reported, internet-based**
Vaz Fragoso et al, **2010 (5)**	**Prospective observational cohort study**	**2b**	**430 older persons non-commercial drivers. Self-reported driving patterns and sleep questionnaires-Insomnia Severity Index (ISI), ESS, and Sleep Apnea Clinical Score (SACS).** **Driving records categorised as a crash or traffic-infraction (composite-I), or as a crash, traffic-infraction, near-crash, or getting lost (composite-II).**	**19.9% (84/422) had high sleep apnoea risk (SACS>15). Drowsy-driving was reported by only 5.1%. Over a ≤ 2 years, 24.9% (104/418) and 51.4% (215/418) of participants had a composite-I and -II driving event, respectively. Insomnia, daytime drowsiness, and high sleep apnoea risk were not associated with a composite-I or –II driving event.**	**Weaknesses: subjective information;** **Information on crashes and traffic-infractions based on self-report and review of driving records from the Connecticut Departments of Motor Vehicles and Transportation**
Vaz Fragoso et	**cross-sectional**	**4**	**430 active drivers aged ≥ 70 years. Questionnaires measured**	**One fifth of the cohort had an SACS > 15, indicating high risk for OSAS. Overall driver self-ratings were**	**Participants predominantly**

al, **2008 (6)**	**survey**		**self-reported insomnia (ISI), drowsiness (ESS), apnoea risk (SACS), driving mileage, driver self-ratings (overall and nighttime), and prior adverse driving events**	**lower in participants with insomnia symptoms, as well as in those with ESS ≥ 10. Sleep disturbances were not associated with an increase in prior adverse driving events**	**male** **subjective information on driving events**
Commercial drivers					
Guglielmi et al, **2018 (7)**	**Cross sectional study**	**4**	**526 truck drivers** **STOP-Bang questionnaire** **Epworth sleepiness scale** **Pittsburgh sleep quality index** **General health questionnaire** **recorded.**	**Half of the sample (269; 51.1%) were at risk for OSA, 19.8% (104) complained of psychological distress, and 17.3% (91) of were bad sleepers, while only 8.9% (47) reported EDS.** **The association between psychological distress and OSA lost significance when low sleep quality and sleepiness were added in logistic regression.**	**Findings were based solely on self-reported data.** **No report on accidents**
Garbarino et al, 2016 (8)	**Cohort study**	**4**	**truck drivers n=949, completed Berlin Questionnaire and ESS, were asked about motor vehicle accidents (MVA) and near misses (NMA)**	**MVA: 34.8% NMA: 9.2%** **OSA predicted MVA (OR 2.32) and NMA (OR 2.39)**	**No verification of MVA**
Zwahlen et al, **2016 (9)**	**Cohort study**	**4**	**128 private and professional drivers** **Questionnaire consisted of 20**	**9% of the participants reported EDS. An equal percentage was at high risk for OSA based on BQ. 16% admitted an involuntary nodding off while driving. This subset of the participants scored statistically**	**Low response rate** **Selection bias**

			questions including ESS, Berlin Questionnaire (BQ)	significant higher on the ESS. No significant difference in BQ between participants with and without involuntary nodding-off. 8% of the participants already suffered an accident secondary to being sleepy while driving. An equal number experienced a sleepiness-related near-miss accident on the road.	No verification of MVA
Ebrahimi et al, 2015 (10)	Cross sectional study	4	556 occupational road drivers Pittsburgh Sleep Quality Index (PSQI) Epworth Sleepiness Scale (ESS) and the 8-question STOP-Bang questionnaire along with demographic information and occupational data were used.	Accident records within the last year and the past 5 years were reported by 6.1% and 23.8%, respectively. ESS (OR = 1.13; 95% CI: 1.07-1.23) and suffering from apnoea (OR = 4.89; 95% CI: 1.07-23.83) were the best predictors for increased risk of MVA.	No verification of MVA
Demirdöğen et al, 2015 (11)	Cohort study	4	Commercial drivers n=282, completed BQ and ESS, were asked about MVA	No significant relationship between past MVA and OSA risk (p=0.197)	No verification of MVA
Barger et al, 2015 (12)	Cohort study	4	Firefighters n=6,933 (92% men, age 40±9 yrs, BMI 28.4±4.3 kg/m2), Berlin Questionnaire, MVA by records	N=1,969 (28%) screened positive for OSA, risk of combined sleep disorder OR 2.00 (p=0.0021) for MVA	No separate analysis for OSA
Catarino et al, 2014 (13)	Cross sectional study	4	Sample of 714 commercial truck drivers; questionnaire (244 face-to-face interviews,470 self-administered) including:	EDS in 20% of drivers, high risk for OSA in 29%. Near-miss accidents reported by 261 drivers (36.6 %; 42.5% of them were sleep related). Driving accidents reported by 264 drivers (37.0 %; 16.3 % of them were	Likely under-reporting of symptoms. Lower desirable

			sociodemographic data, personal habits, previous accidents, ESS, and BQ.	**sleep related).** **ESS score ≥11 was a risk factor for near-miss accidents (odds ratio (OR)=3.84, p<0.01) and accidents (OR=2.25, p<0.01).** **Antidepressant use increased accident risk (OR=3.30, p=0.03).** **Association between Mallampati score III–IV and near misses (OR=1.89, p=0.04).**	**overall rate of response to the questionnaire.** **Self-reported MVA**
Amra et al, 2012 (14)	**cross-sectional survey**	**4**	**Persian commercial drivers (n=931, mean age±SD: 40.2±10.1 yrs), response rate 62% of invited drivers. Self administered questionnaire including: 1) personal information; 2) ESS; 3) BQ, and 4) history of previous MVA.**	**Witnessed apnoea associated with a 2-fold increase (95% CI, 0.98–4.2, P<.04) in the accident rate. High-risk Berlin for OSA associated with an increase in MVA rate to 0.25 (95% CI, 0.07–0.84, P<.02). Neck circumference was also associated with an increase in MVA rate to 0.94 (95% CI, 0.89–0.99, P<.04).**	**Weaknesses: questionnaire-based study; subjective information;** **response to question on MVA not verified by objective** **Police reports.**
Razmpa et al, 2011 (15)	**Cohort study**	**4**	**Bus drivers (n=175, 100% male, age 43±7, BMI 26.4±3.9 kg/m2), self-reported MVA, OSA assessment by ESS and Apnea Index score**	**No correlation between OSA risk and MVA**	**OSA risk assessment based on ESS and a non-validated OSA**

					score
Braeckman et al, 2011 (16)	**Cross-sectional survey**	**4**	**Eligible male truck drivers (n=1580), respondents (n=476), response rate of 30%. Sample recruited with support of Belgian transport federations.** **Self-administered questionnaire including: 1) sociodemographic data; 2) Pittsburgh Sleep Quality Index (PSQI); 3) Epworth Sleepiness Scale (ESS); 4) Berlin Questionnaire (BQ)**	**Mean (SD) PSQI score was 4.45 (2.7); poor quality of sleep (PSQI >5) in 27.2%. The mean (SD) ESS score was 6.79 (4.17); score >10 in 18%. According to BQ, 21.5% had a high risk for OSA. In multiple logistic regression analysis, low educational level (odds ratio [OR] 1.86), current smoking (OR 1.75), unrealistic work schedule (OR 1.75), and risk for OSA (OR 2.97) were independent correlates of EDS.**	**Low response rate (30%); questionnaire-based study; and posible underreporting of health or sleep problems or unhealthy** **lifestyle habits** **No report on accidents**
Vennelle et al, 2010 (17)	**Cross-sectional** **Case-control**	**3b**	**Bus drivers employed within 30 miles of Edinburgh (invited n=1854, respondent n=67, response rate 37%; females: n=25). Sleep questionnaire.** **Controls were 200 consecutive patients referred for sleep studies.**	**Of the responding drivers, 133 (20% of total, 19% of researcher-delivered questionnaires) reported ESS >10. 8% reported falling asleep at the wheel at least once/month, 7% reported an accident, and 18% a near-miss accident due to sleepiness while working.**	**Low rate of volunteering for sleep studies (15%)**

Abbreviations: BQ: BNSQ: Basic Nordic Sleep Questionnaire, Berlin Questionnaire; EDS: excessive dayrtime sleepiness; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; MVA: motor vehicle accidents; NMA: near misses accidents; NMSA: near-miss sleepy accidents; OSA: Obstructive sleep apnoea; PSQI: Pittsburgh Sleep Quality Index; SACS: Sleep Apnea Clinical Score; SD: Standard Deviation.

Table 4. Motor vehicle accidents (MVA) and polysomnography-documented OSA: systematic reviews, studies in non-commercial and commercial drivers, studies in sleep clinic samples

Author	Design	EBM	Patient population	Results	Comments
Systematic reviews and meta-analyses					
Garbarino et al, 2015 (18)	Systematic review	3a	Meta-analysis of 9 studies, risk of MVA	Risk for MVA associated with OSA (AHI>5): median OR 2.83(95% CI: 2.72–3.08). About 7% of total MVA can be attributed to OSA	No dose-effect relationship according to OSA severity
Tregear et al, 2009 (19)	Systematic review	3a	Meta-analysis of 18 studies, only 2 studies related to commercial drivers	Untreated OSA significantly associated with MVA (pooled OR 2.43, p=0.013)	
Ellen et al, 2006 (20)	Systematic review	3a	Forty pertinent studies were identified investigating whether non-commercial and commercial drivers with OSA have increased crash rate	Non-commercial OSA drivers have increased crash rates, with many of the studies finding a 2 to 3 times increased risk. For commercial drivers, only 1 of 3 studies found an increased crash rate, with this association being weak (odds ratio of 1.3).	Mostly male patients; studies heterogeneous for used methodologies
General population					
Gottlieb et al, 2018	Prospective observational	2b	3201 participants (general population)	222 (6.9%) reported at least one motor vehicle crash during the prior year. A higher AHI (p < 0.01), fewer hours of sleep (p = 0.04), and self-	Self-reported MVA

(21)	**cohort study**		**Home polysomnography and questionnaires used to assess history of motor vehicle crashes, usual sleep duration and daytime sleepiness (Epworth Sleepiness Scale)**	**reported excessive sleepiness ($p < 0.01$) were each significantly associated with crash risk. The population-attributable fraction of motor vehicle crashes was 10% due to sleep apnoea and 9% due to sleep duration less than 7 hours.**	
Howard et al, 2004 (22)	**Cohort study**	**4**	**3,268 drivers were invited to complete a questionnaire and anthropometrics. Another sample of 244 drivers also invited to attend in-laboratory PSG**	**More than half (59.6%) of drivers had SDB and 15.8% had OSA, 24%reported excessive sleepiness. Increasing sleepiness was related to an increased accident risk. Those with symptoms of OSA had a higher risk of any MVA , and of a single MVA (OR 1.63, 95% CI 1.08–2.48). In the PSG group, there was no relationship between severity of SDB and MVA risk (OR 0.82, 95% CI 0.15–3.57 for change in RDI of 1 SD).**	**Self-reported MVA**
Shiomi et al, **2002 (23)**	**Cohort study**	**4**	**492 men and 62 women (general population)** **All subjects underwent PSG.** **In addition, a medical history was obtained, including sleeping habits, ESS, and a questionnaire evaluation of MVA during the preceding 5 years.**	**The MVA rate was 3.8% for the 106 simple snorers, 5.8% for the 156 patients with mild OSAHS, 9.9% for the 111 patients with moderate OSAHS, and 11.0% for the 182 patients with severe OSAHS**	

Masa et al, 2000 (24)	**Cohort study**	**4**	**107 sleepy drivers** **109 controls matched by age and sex** **134 accepted PSG**	**The frequency of respiratory sleep disorders was significantly higher in subjects with MVA (the adjusted OR for a total respiratory event index > 15 was 8.5, CI 5 1.2 to 59).**	**Retrospective MVA reporting**
Teran-Santos et al, 1999 (25)	**Case-control study**	**3b**	**102 drivers who had emergency treatment after MVA. Controls: 152 patients randomly selected from primary care centres**	**Compared with those without sleep apnoea, patients with an AHI≥ 10 had an odds ratio of6.3 (95% CI, 2.4 to 16.2) for having a MVA.**	
Young et al, **1997 (26)**	**Cohort study**	**4**	**913 licensed motor vehicle drivers (general population)** **data from 5-year MVA records** **PSG**	**Men with AHI >5, compared to those without sleep-disordered breathing, were significantly more likely to have at least one accident in 5 years (adjusted odds ratio = 3.4 for habitual snorers, 4.2 for AHI 5-15, and 3.4 for AHI > 15). Men and women combined with AHI > 15 were significantly more likely to have multiple accidents in 5 years than control subjects (odds ratio = 7.3).**	
Kingshott et al, 2004 (27)	**Case-control study**	**2b**	**60 motor vehicle crash drivers who had been in a police-reported traffic crash and 60 controls matched for age, gender, and BMI**	**Cases reported significantly higher levels of driver sleepiness (% sleepiness: mean SD; cases: 26 ± 17%; controls: 16 ± 12%; p =0.003) and showed slower reaction times on a sustained attention task (p = 0.02). There was a trend for more objective sleepiness in cases (maintenance of wakefulness test: cases: 17±4 minutes;**	

				controls: 18 ±3 minutes, p =0.06) despite no differences in general subjective sleepiness. **There were no significant differences in PSG measures between groups.**	
Commercial drivers					
Wu et al, **2017 (28)**	**Prospective observational cohort study**	**2b**	**1650 professional drivers** **Basic and working patterns questionnaire, PSQI, ESS, Snore outcomes survey (SOS)questionnaire**	**Road traffic collisions (RTC) drivers had increased ODI4 levels (5.8 ± 4.7 vs 5.0 ± 6.7 events/h; P = 0.008) and ODI3 levels (8.7 ± 6.8 vs 7.4 ± 7.9 events/h; P = 0.007) in comparison with non-RTC drivers. ODI4 and ODI3 levels increased the 6-year RTC risks among professional drivers even after adjusting for confounders**	**No PSG study** **Sleep assessment tools were tested only once, at the beginning of the study** **No treatment status at the end of follow up**
Garbarino et al, 2016 (29)	**Cohort study**	**2b**	**Dangerous goods truck drivers n=283, sleep disorder score used for screening, PSG performed for suspected cases, assessment for MVA and near miss accidents(NMA)**	**Confirmed OSA n=101 (35.7%).** **Severe OSA associated with NMA (OR 4.745)**	**No verification of MVA**
Meuleners et al, 2015	**Case-control**	**2b**	**Truck drivers with MVA in**	**AHI>17 in 31 cases (49%) and 23 controls (35%) (p=0.12). multivariate analysis OSA was**	**Self-reported MVA,**

(30)			**last 12 months n=100** **Truck drivers without MVA n=100** **Limited home study in 63 cases and 65 controls**	**associated with OR for MVA: 3.42 (p=0.01)**	**no oxymetry data**
Karimi et al, 2015 (31)	**Cohort study**	**2b**	**Bus and tram operators** **OSA n=1,478 (70%male, age 54±13 yrs, BMI 29.2±5.5 kg/m2, AHI 17.9 [3.2-24.2])** **Control group from MVA registry (n=21,118)**	**OSA with MVA n=56, increased risk for MVA: 2.45 (p<0.001)**	**CPAP>4 hrs reduced risk**
Stevenson et al, 2014 (32)	**Case-Control**	**2b**	**Heavy-vehicle drivers with MVA (n=530) and without MVA (n=517), MVA verified.** **Objective OSA testing by Flow Wizard**	**Moderate OSA: MVA 18% vs no MVA 14%** **Severe OSA: MVA 13% vs no MVA 16 %** **No association OSA with MVA**	**Drivers experience, driving at night and without break were significant predictors of MVA**
Karimi et al, 2013 (33)	**Cohort study**	**4**	**Bus and tram operators (n=101, 72% male, age 48 [22-64], BMI 27 [16-39])**	**OSA in 25% of the sample. OSA with EDS significantly associated with MVA, but not OSA without EDS**	**Self-reported MVA**
Carter et al, 2003 (34)	**Case-control**	**3b**	**1389 professional lorry and bus male drivers form Sweden; 4000 men in general population in**	**No difference between those with and without reported OSAS.Accidents related to sleep debt.** **Professional drivers had proportionally more**	**Self-perceived sleep debt more important than OSAS**

			Sweden. Questionnaire and PSG in 161 professional drivers.	**sleep debt than non-professionals (p<0.001)**	
Sleep clinic samples and OSA patients					
Matsui et al, **2017 (35)**	**Cohort Study**	**4**	**161 patients with OSA (AHI ≥ 5) who drove on a routine basis and completed study questionnaires. Assessment of sleepiness-related MVA or near-miss events during the prior 5 years**	**68 (42.2%) reported drowsy driving experiences, and 86 (53.4%) reported sleepiness-related vehicular accidents or near-miss events. AHI was not associated with these driving problems.**	**Sampling bias** **Self-reported MVA**
Arita et al, 2015 (36)	**Case-control**	**3b**	**Snorers n=394** **Mild-moderateOSA n=1113** **SevereOSA (AHI>30,<60) n=790** **Very severe OSA (AHI>60) n=484** **All licensed drivers, questionnaire on MVA in the last 5 yrs**	**The group with very severe OSAS reported significantly higher rates of driving when drowsy and having accidents in the past 5 years due to falling asleep**	**ESS only predictor of RTA in multivariate analysis**
Basoglu et al, 2014 (37)	**Case-control study**	**3b**	**312 OSAS patients, 156 age- and sex-matched primary snoring subjects**	**More OSAS patients than snoring subjects reported accidents (21.2% vs. 11.5%, P = .011), and OSAS was associated with an increase in accident risk (odds ratio = 2.06, 95% confidence**	**Retrospective, self-reported questionnaires**

				interval [CI], 1.17 to 3.61, P = .012).Younger OSAS patients (P = .001) and those who were male (P = .001), had greater neck circumference (P = .002), had a higher ESS (P < .0001), and had a higher apnoea–hypopnoea index (AHI; p = .039) had more MVAs	
Ward et al, 2013 (38)	**Cohort study**	**4**	**Clinical cohort evaluated for OSA n=2,673 (63%male, age 50±14 yrs, BMI 32 kg/m2)** **AHI males 31(17-56), females 18 (9-34)** **Self-reported MVA and near-misses**	**OSA OR 3.07 (p<0.001) for MVA but no relationship to near-misses**	**Relationship stronger in men than in women**
Komada et al, 2009 (39)	**Case-control study**	**3b**	**OSA drivers (n=616, 100% male, age 46±10 yrs), Controls: n=600, age-matched**	**MVA OSA vs controls (12.2 vs 4.7%, P<0.001), multivariate analysis AHI>40 OR 1.75 for MVA (P<0.05)**	**Controls had no PSG, MVA unverified, significant reduction in MVA with CPAP**
Mulgrew et al, 2008 (40)	**Case-control study**	**2b**	**783 subjects evaluated for OSA, Control group from insurance database (n=783, age, sex-matched), objective MTA data**	**MVA, OSA n=252, controls n=123.OSA associated with increased risk for MVA, no difference between controls and patients with negative PSG**	**No difference according to OSA severity, no data on OSA in control group**
Lloberes et al, 2000	**Case-control**	**3b**	**189 consecutive patients (sleep clinic population) and**	**122 patients were diagnosed as OSAS and 67 patients as non-apnoeic snorers (NAS). The self-**	**Lack of objective data about traffic**

(41)	**study**		**a control group (CG) of 40 hospital staff workers matched for age and sex with the study population** **Patients underwent a full-night PSG and both patients and the CG completed a questionnaire.**	**reported number of accidents was significantly higher in OSAS patients compared with CG. The self-reported number of times off the road was significantly higher in OSAS patients compared with NAS and with CG. Increased risk for MVA associated with: self-reported sleepiness while driving (OR 5, 95%CI 2.3–10.9), having quit driving because of sleepiness (OR 3, 95%CI 1.1–8.6) and being currently working (OR 2.8, 95%CI 1.1–7.7)**	**accidents, no PSG in controls**
Horstmann et al, 2000 (42)	**Case-control study**	**3b**	**156 patients with sleep apnoea syndrome (SAS) and in 160 age-gender matched controls**	**In the SAS group 12.4% of all drivers had MVA as compared to 2.9% in the control group (p 34/h, n=78) as compared to 1.1 in patients with milder SAS (AHI 10-34/h, n=78) (p<0.05), and 0.78 in control group (p<0.005), respectively.**	
Barbe et al, 1998 (43)	**Case-control study**	**3b**	**60 consecutive patients with SAS (AHI, 58± 3/h) and 60 healthy control subjects, matched for sex and age. Daytime sleepiness (Epworth scale), anxiety and depression (Beck tests), level of vigilance (PVT 192), and driving performance (Steer-Clear)**	**Patients had more MVA than control subjects (OR: 2.3; 95% CI: 0.97 to 5.33) and were more likely to have had more than one MVA (OR: 5.2; 95% CI: 1.07 to 25.29, p < 0.05). These differences persisted after stratification for km/yr, age, and alcohol consumption. Patients were more somnolent, anxious, and depressed than control subjects (p < 0.01), and they had a lower level of vigilance and poorer driving performance (p < 0.01). Yet, no correlation between the risk of MVA in SAS patients and: the degree of daytime sleepiness, anxiety, depression, the number of**	

				respiratory events, nocturnal hypoxemia, level of vigilance, or driving simulator performance.	
Findley et al, **1988 (44)**	**Case-control study**	**3b**	**Driving records of 29 patients with OSA and of** **35 subjects without OSA**	**OSA patients had a 7-fold greater rate of MVA than did the subjects without apnoea ($p < 0.01$).** **The % of persons with ≥ 1 MVA was greater in OSA patients than in controls (31% versus 6%, $p < 0.01$). The % of persons having ≥ 1 accidents in which they were at fault was also greater in OSA patients than in controls (24% versus 3%, $p < 0.02$).The MVA rate of OSA patients was 2.6 times the MVA rate of all licensed drivers in the state of Virginia ($p < 0.02$)**	
Wu et al, **1996 (45)**	**Cohort study**	**4**	**253 patients (sleep clinic population) all studied by PSG and self-reported questionnaire on MVA**	**OSA in 68% of the sample. 82% of those reporting MVA had OSA. Thirty-one percent of patients with OSA compared with 15% of patients without OSA reported at least one MVA ($p < 0.01$). The adjusted OR for MVA analysis was 2.58 for OSA ($p = 0.03$).**	**Other significant factors for MVA were: alcohol intake, falling asleep at inappropriate times, and driving past destination with little awareness**

Abbreviations: AHI: Apnoea hypopnoea index; CG: control group; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; MVA: motor vehicle accidents; NAS: non-apnoeic snorers; NMA: near misses accidents; ODI3; oxygen desaturation index for ≥ 3% desaturation; ODI4: oxygen desaturation index for ≥ 4% desaturation; OR: Odds Ratio; OSA: Obstructive sleep apnoea; OSAHS: Obstructive sleep apnoea hypopnoea syndrome; OSAS: Obstructive sleep apnoea syndrome; PSG: Polysomnography;

PSQI: Pittsburgh Sleep Quality Index; PVT: Psychomotor vigilance test; RTC: Road traffic collisions; SD: Standard Deviation. SOS: Snore outcomes survey questionnaire.

Table 5. Predictors of excessive daytime sleepiness in obstructive sleep apnoea patients.					
Author	**Design**	**EBM**	**Population**	**Results**	**Comments**
Mendelson, 1995 (46)	**Retrospective study in subjects with suspected SDB at diagnosis**	**4**	**518 OSA patients studied by full PSG, MSLT and subjective sleepiness questionnaire.**	**At multiple regression analysis, 64% of subjective EDS variance accounted for by body weight; 71% of MSL accounted for by lowest SpO2 in non-REM sleep**	**EDS assessed in a heterogeneous sample with SDB**
Zamagni et al, 1996 (47)	**Subjects randomly selected out of a Sleep Clinic sample of subjects with suspected OSA**	**2b**	**44 subjects with obstructive SDB of variable severity, full PSG with oesophageal pressure (Pes) recordings, modified MSLT, EDS evaluated by French adaptation of Basic Nordic Sleep questionnaire**	**Mean sleepiness score: 9.7, mean sleep latency 13.9 min. Mean maximal end-apnoeic Pes 49 cmH2O. At multiple regression analysis, independent contributors were for sleepiness score: apnoea index and Pes variables; for MSL: daytime $PaCO_2$ and indexes of nocturnal hypoxemia. No correlation with indexes of sleep fragmentation**	**Only subjective EDS correlated with respiratory effort.**
Bennett et al, 1998 (48)	**Subjects randomly selected out of a Sleep Clinic sample of subjects with suspected OSA**	**2b**	**40 subjects with obstructive SDB of variable severity, full PSG with assessment of sleep fragmentation, ESS, OSLER, MWT before and after CPAP**	**Baseline data: all sleep fragmentation indices, AHI and SpO_2 dip rate significantly associated with ESS scores** **Post-CPAP improvement in subjective (Epworth) and objective (OSLER) sleepiness best predicted by ODI 4%.**	

Leng et al, 2003 (49)	**Retrospective consecutive case series, Asian patients with suspected OSA**	**4**	**72 patients, 41 OSA (AHI >5)** **Subjective EDS = ESS** **Obiective EDS: non-sleepy: MSLT > 10 min; moderately sleepy 5-10 min; very sleepy <5 min**	**At multivariate analysis, mean sleep latency on MSLT negatively associated with ESS score ≥8 and AHI**	**EDS assessed in a heterogeneous sample with EDS**
Seneviratne et al, 2004 (50)	**Retrospective, study in Asian OSA patients**	**4**	**195 OSA (89.4% males) patients studied by PSG and MSLT** **EDS: mean sleep latency (MSL) on MSLT (no EDS: MSL ≥10 min; EDS: MSL< 10 min)**	**Independent predictors of EDS: high sleep efficiency, number of total arousals, and severity of snoring**	**Sleep efficiency possibly reflecting longer sleep time in patients with EDS**
Goncalves et al, 2004 (51)	**Prospective study in patients with suspected OSA**	**2b**	**135 male subjects, full PSG, ESS, BDI, SF-36, report of driving accidents**	**Mean ESS score in the sample: 15.1. ESS correlated with: arousal index, AHI and lowest SpO2. At multivariate analysis, age and AHI remained significant, explaining 41% of ESS variance. No variable was significant predictor of driving accidents**	
Bixler et al, 2005 (52)	**Prospective population study on determinants of EDS**	**2b**	**Over 16,000 subjects undergoing questionnaire, over 1700 studied by PSG. EDS assessed by questionnaire.**	**Prevalence of EDS in the whole population: 8.7%. Risk factors depression, BMI, age, sleep duration, diabetes, smoking and sleep apnoea. Peak OR EDS in subjects <30 yrs and elderly. EDS not associated with any polysomnographic parameter.**	

Kapur et al, 2005 (53)	**Retrospective cross-sectional population study (SHHS)**	**2b**	**1149 OSA, full PSG** **EDS= Epworth Sleepiness Scale score >10 or a report of at least frequently feeling unrested or sleepy.**	**Sleepiness in about half of the sample, increasing with OSA severity. EDS associated with: self-reported short sleep duration, complaints of not getting enough sleep, respiratory disease, sleep maintenance insomnia, early morning awakening, habitual snoring, and awakening with leg cramps or jerks.** **Sleepiness associated weakly with AHI, no association with sleep time, sleep efficiency, sleep stage distribution, or arousal index.**	**EDS classified based on Epworth and more liberal definitions. Highlights the role of comorbidities, role of depression not tested.**
Mediano et al, 2007 (54)	**Cross-sectional study in Caucasian OSA patients**	**2b**	**40 patients with severe OSA undergoing full PSG and MSLT. EDS defined as ESS score >10 and MSLT score < 5 min.** **No EDS (n=17) defined as ESS score <10 and MSLT >10 min; EDS (n=23) defined as ESS score >10 and MSLT <10 min**	**Both MSLT and ESS score correlated with mean and lowest nocturnal SpO_2, and high sleep efficiency. No differences in arousal index or overall distribution of sleep stages between the two groups.**	

Barcelo et al, 2008 (55)	**Case-control study in OSA patients**	**3b**	**44 OSA patients studied by full PSG, MSLT, ESS and metabolic assessment (glucose, insulin, HOMA, lipids, TSH, cortisol, GH, IGF-1). 23 controls studied by cardiorespiratory polygraphy, ESS and metabolic assessment.** **EDS: ESS >10, MSL<5 min; no EDS: ESS<10 and MSL>10 min** **EDS+ and EDS- groups matched for age, BMI, and AHI.**	**Insulin resistance (HOMA) significantly related to MSLT and ESS, and lowest nocturnal SpO_2. Positive effects of CPAP treatment on metabolic variables only in sleepy patients.**	
Roure et al, 2008 (56)	**Multicentre cross-sectional study in Caucasian OSA patients**	**2b**	**2882 patients with AHI >5, EDS defined as ESS score >10 (EDS+ n=1649; no EDS n=1233)** **Evaluation of PSG variables**	**Patients with EDS exhibited overall longer TST and shorter sleep latency, greater sleep efficiency, reductions in NREM sleep stages 1-2 and longer SWS. A lower SaO_2 nadir, and greater AHI and arousal index were also found in sleepy patients.**	
Koutsourelakis et al, 2008 (57)	**Prospective study in subjects with suspected OSA**	**2b**	**915 subjects studied by full PSG, ESS, BDI and clinical characteristics including comorbidities**	**ESS >10 in 38.8% of the sample. RDI, depression and diabetes main correlated of ESS score at multivariate analysis. Minor significant contributions by: COPD, stroke,**	

				heart disease alcohol use, and BMI.	
Bausmer et al, 2010 (58)	Retrospective study of OSA patients with ENT pathology	4	130 patients studied by full PSG and ESS	No ESS data reported, only lack of correlation between sleep variables and ESS, with the exception of a weak relationship with arousal index.	
Oksenberg et al, 2010 (59)	Retrospective cohort study in Caucasian OSA patients	2b	644 severe OSA (AHI ≥30). EDS defined as ESS >10 (data in 88.3% of the sample).	Sleepy patients were slightly younger and more obese, and showed shorter sleep latency and SWS compared to non-sleepy patients. Total recording time, Arousal Index and minimum SaO_2 during sleep differed significant between sleepy and non-sleepy patients. Comparing sleepy with very sleepy patients (ESS ≥16), Apnoea Index was the most significant contributing factor for EDS.	
Ishman et al, 2010 (60)	Case-control study	3b	47 OSA patients, 6 snorers, 51 controls. Full PSG, ESS, BDI-II	ESS not correlated with OSA severity, but direct relationship with BDI-II score	
Chen et Al, 2011 (61)	Retrospective study in Chinese patients with suspected OSA	2b	1035 consecutive OSA patients studied by full PSG. 249 snorers (AHI<5); 225 mild OSA (AHI 5-20); 171 moderate OSA (AHI >20-40); 390 severe OSA (AHI >40). Variables analyzed: daytime sleepiness (ESS>10), total sleep time (TST), sleep	ESS correlated with BMI, AHI, ODI, with the strongest association for ODI. Positive trend between ESS and time spent at SpO_2<90%. No correlation of ESS with sleep structure	

			stages, respiratory arousal index, time SpO_2<90%; lowest SpO_2, ODI. Linear and stepwise multiple regression.		
Sanchez-de-la Torre et al, 2011 (62)	**Case-control study in OSA patients with and without EDS**	**3b**	**264 patients studied by full PSG, ESS, and evaluation of plasma hypocretin-1, neuropeptide Y, leptin, ghrelin, and adiponectin. EDS group (ESS≥13, n=132) and no-EDS group (ESS≤9, n=132) matched for gender, BMI, and AHI.**	**Patients with EDS showed higher hypocretin-1 and lower ghrelin than patients without EDS.**	
Sun et al, 2012 (63)	**Cross-sectional study, Chinese OSA patients**	**4**	**80 OSA patients studied by full PSG (AHI>5), MSLT, and ESS.** **EDS (n=32): ESS >10 and MSLT score <5 min; no EDS (n=48)**	**Arousal index, time spent at SaO_2 <95%, and REM sleep latency were independent predictors of EDS. More severe OSA in sleepy patients**	
Pamidi et al, 2011 (64)	**Cross-sectional study in OSA patients at diagnosis**	**2b**	**931 patients studied by PSG; REM-related OSA (AHI-REM/AHI-NREM≥2, REM duration > 10.5 min, and AHI-NREM < 8): n=126;**	**No differences in ESS score between REM-OSA and non-REM OSA. AHI-NREM was predictive of ESS in the entire cohort of patients.** **In REM-related OSA, BMI and CES-D score were significant predictors of ESS and PCS-12**	**Depression and obesity predicted ESS better than OSA severity**

			non-stage specific OSA: n=805. **ESS, Center for Epidemiologic Studies Depression Scale (CES-D) , and short-form quality of life questionnaire-12 (SF-12, mental [MCS-12] and physical component summaries [PCS- 12]**	**score.** **No relation of ESS with AHI-REM or AHI-NREM.**	
Bonsignore et al, 2012 (65)	**Retrospective study in OSA patients**	**4**	**529 patients studied by full PSG, ESS, and metabolic assessment (Metabolic syndrome, MetS)**	**No difference in prevalence of EDS according to presence of MetS or insulin resistance. Age and mean nocturnal SpO_2 negatively associated with EDS.**	
Cai et al, 2013 (66)	**Retrospective study, Chinese patients with suspected OSA**	**4**	**80 OSA patients studied by full PSG (AHI>5), MSLT (EDS if sleep latency<10 min), and ESS (EDS if score>10).**	**MSLT<10 min in 56 patients, ESS >10 in 71 patients. Mean sleep latency (MSL) and ESS correlated with ODI, lowest SpO_2, arousal index, AHI, sleep efficiency and TST.** **Only MSL correlated with non-REM phase 1+2%, SWS and REM sleep latency.**	**Only 68% of the sample reported driving, with possible ESS underestimation**

Rey De Castro et al, **2013 (67)**	**Cross-sectional study in OSA patients**	**4**	**151 OSA studied by full PSG.** **No EDS: ESS≤10; EDS: ESS>10; severe EDS: ESS≥16**	**ESS >10: 66 patients (44% of the sample); ESS ≥16: 23 patients (21%). Patients with OSA and EDS showed more severe hypoxemia than OSA without EDS, but the correlation between EDS and hypoxemia became not statistically significant at multivariate analysis.** **No correlation between EDS and polysomnographic variables.**	**Respiratory events defined according to American Sleep Disorders Association (ASDA) 1992**
Jacobsen et al,2013 (68)	**Retrospective, cross-sectional study**	**4**	**355 patients with severe OSA studied by full PSG, analysed according to ESS quartiles; lowest (ESS≤ 6: n=105) and highest (ESS ≥ 13: n=97) quartiles were compared.** **ODI, SpO_2 nadir, AHI evaluated.** **Patients with diagnosis of depression or treated with hypnotics, benzodiazepines, or antidepressants were excluded.**	**Compared with ESS ≤ 6, ESS ≥ 13 have lower SpO_2 nadir and higher ODI.** **Trend for higher AHI in sleepy patients.** **Higher CES-D questionnaire scores in sleepy patients despite exclusion of patients with depression.**	

Slater et al, 2013 (69)	**Retrospective study**	**4**	**335 patients studied by full PSG** **155 obese (BMI >30)** **173 OSA (AHI >5/h)(61 on CPAP treatment)** **55 with PLM disorder** **EDS defined by ESS >10**	**Obesity (but not BMI), PLM disorder and hypertension were independently associated with ESS score. AHI was predictor of sleep latency on PSG.**	**Slater et al. 2013**
Uysal et al, **2014 (70)**	**Cross-sectional study**	**4**	**N: 200 AHI≥15** **EDS: EES≥ 10, no EDS: ESS <10** **Hypoxemia variables combined in a hypoxemia biomarker: ODI, average % oxygen desaturation, % of time with oxygen saturation <90%, lowest % oxygen saturation**	**The hypoxemia biomarker predicts EDS only in patients with severe OSA (AHI>50)**	**The hypoxemia variables do not predict EDS when not combined in the biomarker.**
Huamanì et al, **2014 (71)**	**Retrospective study in OSA patients**	**2b**	**N: 518 with AHI≥5 and ESS (EDS= ESS >10). Analysed variables: nocturnal hypoxemia (NH) byT90 and Maximum arterial oxygen desaturation (MOD):**	**ESS>10 in 50.6% of OSA patients; NH in 87.2% of OSA patients.** **EDS associated with nocturnal hypoxemia (NH).** **Higher probability of sleepiness in patients**	**Only men included. Studied conducted at high altitude (Lima, Peru) any environmental**

			Categories: **no NH: T90=0%, MOD=0** **NH <1%: MOD indicates NH but T90=0%** **NH 1-10% 1<T90>10%** **NH>10%: T90 >10%**	**with NH>10%**	**effect on nocturnal hypoxemia?**
Corlateanu et al,2015 (72)	**Cross-sectional study in consecutive OSA patients**	**4**	**50 subjects, respiratory polygraphy, ESS. Linear and multiple regression models.**	**EDS in 38% of the sample. Oxygen Desaturation index predicted EDS better than AHI. No effect of anthropometrics**	
Adams et al, 2016 (73)	**Cross.sectional study in community-dwelling men (MAILES Study)**	**2b**	**837 subjects, studied by full PSG, ESS, STOP and PSQI, and a EDS alternate definition (EDSalt: ≥2 of the following: feeling sleepy sitting quietly, feeling tired/fatigued/sleepy, and trouble staying awake)**	**ESS≥11 in 12.1% of the sample. No effect of OSA severity or BMI, or sleep variables by ESS status. At multivariate adjusted analysis, EDS associated with nocturia and depression.** **By using EDSalt definition, EDS in 30.4% of the sample. Increased adiposity, diabetes depression, nocturia, indices of severe OSA associated with EDSalt. At multivariate adjusted analysis, EDS associated with depression, physical inactivity, short sleep, social factors, and highest quartile of arousal index.**	**Interesting study, suggests different dimensions of EDS with different instruments of EDS evaluation.**

Ryu et al, 2016 (74)	**Retrospective study in moderate-severe OSA patients in Korea**	**2b**	**559 subjects, studied by full PSG, ESS, and Sleep Breathing Scale (SBS, subjective assessment of OSA severity), Beck Depression Inventory (BDI)**	**ESS score≥11 in 40.6% of the sample.** **At univariate analysis, ESS associated with SBS score, AHI, lowestSpO2, BMI, and BDI score. In multiple regression analysis, only SBS and BDI score correlated with ESS.**	
Huang et al, 2016 (75)	**Cross-sectional study in severe OSA patients (AHI≥30)**	**4**	**175 subjects studied by full PSG, 119 with and 56 without EDS (ESS≥10)**	**Significant correlations between ESS score and components of MetS, including SBP, waist circumference, log TG, HDL-C, log fasting glucose and metabolic score. At multivariate analysis ESS score, log insulin and age significantly predicted the metabolic score**	
Lang et al, 2017 (76)	**Cross sectional study in urban community dwelling men**	**2b**	**788 randomly selected, men aged 40 to 88 yrs without a prior diagnosis of OSA. Full PSG at home, EDS: ESS>10**	**Depression associated with AHI>30. Individuals with mild–moderate or severe OSA and EDS exhibited increased probability of depression compared to individuals with either condition alone**	**Object of the study is depression, not EDS**
Kim SA et al, 2017 (77)	**Cross sectional study in OSA**	**2b**	**633 OSA patients diagnosed by PSG. Relationship between EDS assessed as ESS>10 and Fatigue Severity Scale (FSS)**	**ESS and other variables correlated with FSS. FSS score is more likely to be associated with younger age, sleepiness and insomnia, but less likely to be directly related to OSA severity**	**About fatigue, not EDS**
Martynowicz et al, 2017 (78)	**Cross sectional, case-control study in hypertensives (HT) and**	**3b**	**304 HT and 67 NT. Full PSG and ESS**	**In hypertensives >AHI, ODI and %NREM2, <SEI and %SWS. In the moderate to severe OSA groups, the total ESS score was significantly lower in HT compared with NT. The ESS scores**	

	normotensives (NT)			**decreased with age in HT, but not in NT**	
Kim H et al, 2017 (79)	**Cross sectional study in a sample from Korean general population (KoGES cohort)**	**2b**	**711 mild OSA (AHI 13.35±8.85) and 781 non-OSA subjects, studied by PSG. EDS assessed as ESS>10**	**Mean ESS score in the entire sample: 5. Mild significant differences between OSA and non-OSA subjects in Digit Symbol Test and in ESS, but substantially preserved cognitive function and QoL. Similar performances and QoL in sleepy (6.3% of the OSA sample) and non-sleepy OSA subjects. Hypoxia was mild and did not correlate with cognition.**	
Li Y et al, 2017 (80)	**Cross sectional study in OSA patients**	**4**	**58 untreated OSA patients, PSG for 4 consecutive nights, Psychomotor vigilance test (PVT), MSLT and ESS**	**PVT results correlated with ESS but not MSLT or IL-6. Suggests that ESS and PVT may be useful in predicting risks associated with impaired performance, such as traffic accidents, in patients with OSA.**	**Same pts sample as in Li Y Sleep 2017**
Li Y et al, 2017 (81)	**Cross-sectional study in OSA patients**	**2b**	**58 patients (AHI≥10 women, ≥15 men) studied by full PSG for 4 nights; MSLT, and Stanford Sleepiness Scale (SSS) on the morning of 4th day;24-h blood samples to assess cortisol and interleukin-6 (4th day). Beck Depression Inventory II (BDI-II) also assessed**	**MSL positively associated with 24-h IL-6 levels, and negatively associated with cortisol levels. ESS or SSS did not show any significant correlation with EDS.**	

Chen YC et al, 2017 (82)	**Cross sectional study in patients with primary snoring, moderate-severe OSA, very severe OSA**	**4**	**Genome-wide gene expression array in PBMC of patients studied by PSG. Sleepiness assessed as ESS>10.**	**Expression of the protein P130 (AMOt gene, angiomotin variant 2, related to endothelial tight junction) increased in OSA, especially if associated with EDS**	**Small study, data should be confirmed by larger studies.**
Fu et al, 2017 (83)	**Cross-sectional study in newly diagnosed OSA patients**	**2b**	**2241 men with suspected OSA studied by PSG, mean age 40 yrs, mean BMI 26.9 kg/m^2. Sleepiness assessed by ESS. Correlation between EDS and Metabolic Syndrome**	**Degree of obesity and ESS scores highest in severe OSA and significantly associated with metabolic syndrome, especially with increased fasting blood glucose.**	
Prasad et al, 2018 (84)	**Cross-sectional study in newly diagnosed OSA patients**	**2b**	**283 patients with AHI≥5 and age 35-60 yrs. Sleepiness assessed by ESS≥11 (subjective) and psychomotor vigilance test ≥2 lapses (objective). Chronotype assessed by actigraphy. Plasma TNF-alpha and IL-6**	**Sample divided in 4 groups (subjective and objective sleepiness; objective sleepiness only, subjective sleepiness only, no sleepiness). African-American race and short daily sleep associated with increased EDS, morningness protective. IL-6, but not TNF, associated with EDS.**	**No control for depression or socioeconomic factors.**
Goh et al, 2018	**Retrospective study in suspected OSA**	**2b**	**821 suspected OSA with AHI ≥5. PSG and ESS**	**Age, apnoea load, REM, NREM 1 correlated to ESS independently but weakly. AHI not correlated**	**Apnoea and hypopnoea load as measured by**

					their total durations
D'Rozario et al,2018 (85)	**Cross sectional, case-control study in OSA and non-OSA subjects**	**3b**	**204 untreated OSA pts and 50 non-OSA studied by PSG, ESS and a test battery including assessment of selective attention, executive function, working memory and sustained attention task (psychomotor vigiliance test, PVT)**	**OSA patients showed worse cognitive, executive and working memory performance, and worse performance at PVT. High ESS was associated with slower performance at PVT. AHI or EEG arousal index not correlated with any performance measure, hypoxemia significantly associated with worse executive function**	
Nigro et al, 2018 (86)	**Retrospective analysis in OSA patients**	**2b**	**1084 untreated OSA patients studied by PSG, 46.5% women. EDS: ESS>10**	**EDS reported more frequently by men (42%) than by women (32%) with OSA. At multivariate logistic regression, predictors of EDS were: younger age, BMI, AHI, mean SaO_2, lack of insomnia, and tiredness.**	**Study on influence of gender on OSA symptoms**

Abbreviations: AHI: Apnoea hypopnoea index; BDI: Beck Depression Inventory; BMI: Body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; COPD: Chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; EEG; electroencephalogram; EDS: excessive daytime sleepiness; ENT: Ear, Nose, and Throat; ESS: Epworth Sleepiness Scale; FSS: Fatigue Severity Scale; HT: hypertensives; MOD: Maximum arterial oxygen desaturation; MetS: Metabolic syndrome; MSL: mean sleep latency; MSLT: mean sleep latency test; MWT: Maintenance of Wakefulness Test; NH: nocturnal hypoxemia; NT: normotensives; ODI; oxygen desaturation index; ODI4: oxygen desaturation index for ≥ 4% desaturation; OR: Odds Ratio; OSA: Obstructive sleep apnoea; Pes: oesophageal pressure; PLM: Periodic limb movement; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; PVT: Psychomotor vigilance test; QoL: Quality of life; RDI: Respiratory Disturbance Index; SBP: Systolic Blood Pressure; SDB: Sleep Disorder Breathing; SF:

short-form quality of life questionnaire; SHHS: Sleep Heart Health Study; SpO_2: Oxygen saturation; SBS: Sleep Breathing Scale; SSS: Stanford Sleepiness Scale; TST: Total sleep time.

Table 6. Predictors of excessive daytime sleepiness in obesity					
Author	**Design**	**EBM**	**Population**	**Results**	**Comments**
Ng et al, 2017 (87)	**Meta-analysis on effects of intentional weight loss on EDS**	**1a**	**42 studies, surgical weight loss (n=15), non-surgical weight loss (n=27, 15 RCT)**	**Larger weight loss after surgical than nonsurgical intervention, associated with decreased EDS (non-linear dose-response relationship). No relationship between EDS changes and AHI changes**	
Vgontzas et al, 1998 (88)	**Case-control study. Obese patients with SDB excluded by study design**	**3b**	**73 obese subjects without SDB, 45 age matched control. PSG for 8 h at night, and 2 1-h daytime naps. Daytime sleepiness assessed clinically (no ESS) and based on the results of nap studies.**	**Daytime sleepiness reported by 57% of obese subjects and 2% of controls. Worse nocturnal sleep amount and quality in obese patients, suggesting a circadian abnormality in obese patients.**	
Resta et al, 2001 (89)	**Consecutive obese patients recruited in Endocrinology Clinic**	**2b**	**161 obese patients studied by full PSG (more than 50% BMI over 40). Sleep and Health Questionnaire and ESS. No OSA: AHI<10**	**EDS reported by 35% of obese patients without OSA. No correlation between EDS with BMI, age, or RDI in this subpopulation**	

Resta et al, 2003 (90)	**Case-Control study**	**3b**	**78 severely obese patients without OSAS,** **40 healthy sex- and age-matched normal** **weight subjects; PSG in both groups, modified version of the Sleep and Healthy questionnaire, and the ESS** **Variables evaluated: BMI, neck circumference, waist-to- hip ratio(WHR) ,RDI ,TST, SaO2 < 90%** **Sleep latency,REM sleep percentage ,REM latency , Sleep efficiency, Arousal index (AI)**	**EDS prevalence: 35%, in the obese non-OSA group, 3% in controls. In obese patients, no correlation between ESS score and age, BMI, neck circumference, RDI, arousal index and sleep variables. Those reporting loud snoring had higher ESS score than those who did not have this symptom and ESS score increased progressively with the severity of reported snoring.**	
Dixon et al, 2005 (91)	**Longitudinal study in severely obese patients undergoing laparoscopic adjustable gastric banding (LAGB)**	**4**	**25 patients studied by full PSG and ESS before and 18 months after LAGB**	**LAGB decreased body weight, ESS, and AHI. Improved QoL and depression**	**No analysis on mechanisms for ESS reduction after LAGB, small sample**

Dixon et al, 2007 (92)	**Cohort studyin patients undergoingobesity surgery (BMI >35 kg/m^2)**	**2b**	**ESS administered to 1055 consecutive patients;** **331 at high risk for OSA performed PSG, no OSA (AHI <5):n=70, OSA: n=261** **Variables evaluated: EDS by ESS scores, anthropometrics and sleep variables, QoL (SF-36) and Beck Depression score**	**ESS score<10 in 50% of the PSG sample. No relation between ESS and BMI, AHI, arousal index, sleep efficiency, sleep fragmentation, apnoea hypopnoea length, oxygen desaturation, periodic leg movements. High fasting plasmaglucose, low HDL-cholesterol,hyperinsulinemia and presence of type 2 diabetes were associated with higher ESS scores.** **Symptoms of depression, poor quality of life, and patient-reported nocturnal sleep disturbance also correlated with EDS.**	
Nerfeldt et al, 2010 (93)	**Nonsurgical weight loss program in OSA patients**	**4**	**33 patients undergoing a 8-wk hypocaloric diet, and a support program for 2 years, + treatment with CPAP (in 19 pts) or MAD (in 4 pts)**	**Limited effect of weight loss on AHI, but decreased weight correlated with decreased ESS and insulin levels.**	
Sharkey et al, 2013 (94)	**Retrospective studyin patients candidate to**	**4**	**269 patients (239 females) studied by full PSG, ESS, and FOSQ.**	**Average AHI: 29.5±31.5/h, mean ESS score: 6.3±4.8; mean global FOSQ score**	**Low self-reported sleepiness**

	bariatric surgery		**EDS defined as ESS ≥10**	**100±18. AHI did not correlate with ESS score.**	
Koehler et al, 2014 (95)	**Retrospective cohortstudy**	**4**	**245 obese OSA (BMI>35 and AHI>15/h) studied by full PSG** **EDS: ESS score ≥ 11**	**ESS>11 in 50.2% of the sample. Sleepy patients were younger and showed more severe OSA than non-sleepy ones. Decreased mean SpO2 during sleep and time spent atSpO2 below 80 % were independent predictors of EDS.**	
Valencia-Flores et al, 2015 (96)	**Cross-sectional studyin patients living at moderate altitude (Mexico City)**	**4**	**78 obese subjects (23 F, 55 M)** **OSA defined as AHI ≥5 events/h** **Alertness defined using Maintenance Wakefulness Test (MWT) as a mean sleep latency of ≥ 12 min.**	**ESS>10 in 17% of F, and 36% of M. ODI and SpO2 nadir were significantly and independently associated with MWT**	
Fernandez-Mendoza et al, 2015 (97)	**Longitudinal population study (Penn Cohort)**	**2**	**1395 subjects studied by full PSG and sleepiness questionnaire at baseline and followed for 7.5 yrs. Factors associated with persistent, incident or remitted EDS**	**Obesity and weight gain associated with incidence and persistence of EDS, weight loss associated with EDS remission. Depression and comorbidities also investigated and involved in natural history of EDS**	

Ng et al, 2017 (87)	**Longitudinal analysis (SHHS data)**	**2**	**1468 subjects studied by full PSG and ESS at baseline and followed for 5 yrs. Complex statistical analysis to assess the relationship between weight changes and changes in ESS**	**ESS at follow-up worsened by 0.36 units with every 10-kg weight gain. The effect was significant only in women and about 20% of this effect was mediated by OSA severity at 5 years.**	

Abbreviations: AI: Arousal index; AHI: Apnoea hypopnoea index; BMI: Body mass index; CPAP: continuous positive airway pressure; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; LAGB: laparoscopic adjustable gastric banding; MAD: Mandibular Advancement Devices; MWT: Maintenance of Wakefulness Test; ODI; oxygen desaturation index; OSA: Obstructive sleep apnoea; OSAS: Obstructive sleep apnoea syndrome; PSG: Polysomnography; QoL: Quality of life; RDI: Respiratory Disturbance Index; SDB: Sleep Disorder Breathing; SF: short-form quality of life questionnaire; SpO2: Oxygen saturation; TST: Total sleep time; WHR: waist-to- hip ratio.

Table 7. OSA screening questionnaires: meta-analyses

Author	Design	EBM	Objectives and Patient population	Results	Comments	Observations for the future
Ramachandran et al, 2009 (98)	Systematic review and Meta-analysis	2a Cohort studies	To compare clinical screening tests for OSA and to establish an evidence base for their preoperative use.	26 studies (n=6794 patients with suspected OSA) met the inclusion criteria: 8 studies on questionnaires and 18 studies on algorithms, regression models and neural networks. Test accuracy in repeated validation studies of the same screening test is variable, suggesting an underlying heterogeneity in either the clinical presentation of OSA or the measured clinical elements of these models. The Berlin questionnaire and the Sleep Disorders Questionnaire were the two most accurate questionnaires. Predicting the diagnosis of OSA : - Pooled sensitivity 52% - Pooled specificity 80% Predicting the diagnosis of severe OSA :	Based on the false-negative rates, it is likely that most of the clinical screening tests will miss a significant proportion of patients with OSA.	BIASES : Significant differences between the validation study patients and surgical patients.

				- **Pooled sensitivity 86%** - **Pooled specificity 68%**		
Abrishami et al, 2010 (99)	**Systematic review and Meta-analysis**	**2a Cohort studies**	**To identify and evaluate the available questionnaires for screening OSA.**	**10 studies (n =1484 patients) met the inclusion criteria. The Berlin questionnaire was the most common questionnaire (four studies) followed by the Wisconsin sleep questionnaire (two studies).** **In "sleep disorder patients":** - **Pooled sensitivity 72.0%** - **pooled specificity 61.0%.** **In "patients without history of sleep disorders":** - **Pooled sensitivity 77.0%** - **pooled specificity 53.0%.**	**STOP and STOP-Bang questionnaires had the highest methodological quality.**	**Inconsistency in results could be due to studies with heterogeneous design (population, questionnaire type, validity).**
Nishiyama et al, 2014 (100)	**Meta-analysis**	**2a Cohort studies**	**To summarise the evidence for criterion validity of the ESS for the diagnosis of**	**N=367 patients, no detailed anthropometric data for the whole group.**	**For ESS>10 :** **AHI≥5 :** **Sensitivity : 32%**	**ESS not highly accurate for predicting OSA. ESS has no value in identifying OSA.**

			OSA, PLMD, RBD, and narcolepsy, by meta-analysis, combining the current and previous studies.		**Specificity : 69%** **AHI≥15 :** **Sensitivity : 31%** **Specificity : 64%**	
Nagappa et al, 2015 (101)	**Systematic review and Meta-analysis**	**2a** **Cohort studies**	**To determine the effectiveness of STOP-Bang for screening patients suspected of having OSA and to predict its accuracy in determining the severity of OSA in the different populations.**	**17 studies (n=9206 patients) were included for systematic review (11 studies in sleep clinic populations, 3 studies in surgical population, 1 study in general population, 1 study in highway bus drivers, and 1 study in renal failure patients).** **Pooled predictive parameters of STOP-Bang ≥3 as cut-off in sleep clinic population (for AHI≥5 ; AHI≥15 ; AHI≥30)** - **sensitivities : 90%, 94%, 96%** - **Specificities : 49% ; 34%, 25%** **Pooled predictive parameters of STOP-Bang ≥3 as cut-off in surgical population (for AHI≥5 ; AHI≥15 ; AHI≥30)** - **sensitivities : 84%, 91%, 96%**	**The STOP-Bang questionnaire has been validated as an excellent screening tool for OSA in sleep clinic and surgical population.**	**Data in other populations is limited (general population, drivers, chronic kidney disease).**

				- Specificities : 43% ; 32%, 29%		
Chiu et al, 2017 (102)	Systematic review and Meta-analysis	2a Cohort studies	To investigate and compare the pooled sensitivity, specificity, and diagnostic odds ratio (DOR) among the BQ, SBQ, STOP, and ESS according to the severity of OSA.	108 studies (n=47989 patients) met the inclusion criteria. The performance levels of the Berlin questionnaire, STOP-Bang questionnaire, STOP, and ESS in detecting OSA of various severity levels are: - for mild OSA: the pooled sensitivity levels were 76%, 88%, 87%,and 54%; the pooled specificity levels were 59%, 42%, 42%, and 65%. -for moderate OSA: the pooled sensitivity levels were 77%, 90%, 89%, and 47%; the pooled specificity levels were 44%, 36%, 32%, and 621%. -for severe OSA: the pooled sensitivity levels were 84%, 93%, 90%, and 58%; the pooled specificity levels were 38%, 35%, 28%, and 60%.	The sensitivity of the STOP-Bang questionnaire was higher than that of other questionnaires for detecting mild, moderate, and severe OSA. Compared with ESS, the STOP-Bang has limited value in screening out patients without OSA. The risk of bias in most domains was unclear, because of insufficient details in the reported data.	Sample size affected the results, i.e. lower sensitivity for the STOP and ESS in studies on <200 compared to those on ≥200 subjects. The diagnostic properties of the questionnaires for some populations (e.g. Epworth in surgical patients, STOP-Bang in patients with cardiovascular and respiratory diseases, and STOP and ESS in community or general population) were unavailable.
Senaratna et al,	Systematic review and	2a	To report the Berlin	35 studies met the inclusion criteria.		Need for consensus on consistent

2017 (103)	**Meta-analysis**	**Cohort studies**	**questionnaire's diagnostic utility as measured against type-1 PSG. The sensitivity was higher when hypopnoea was defined as ≥3% oxygen desaturation rather than >4% . No such relationship with hypopnoea definition was seen for specificity.**	**In sleep clinic population : Pooled sensitivity ranged from 79% to 82%.** **Pooled specificity ranged from 32% to 39%.** **In patients with cardio- or cerebro-vascular disease or risk factors :** ***Pooled sensitivity* ranged from 40% to 93%.** ***Pooled specificity* ranged from 26% to 76%.** **In the general population :** **For an AHI≥5 :** ***Pooled sensitivity* ranged from 37% to 69%.** ***Pooled specificity* ranged from 83% to 84%.** **For an AHI≥10 :** ***Pooled sensitivity* 79%** ***Pooled specificity* 67%** **For an AHI≥15 :** ***Pooled sensitivity* ranged from 43% to**		**definitions for gold-standard PSG to measure and diagnose OSA. In addition, reporting the diagnostic utility for multiple reference standards and for multiple AHI thresholds could help make valid comparisons between different validation studies. More validation studies are needed using the Berlin questionnaire in primary care and in the general population (including comparison to other OSA screening tools).**

				89%. ***Pooled specificity*** **ranged from 63% to 80%.** **In surgical population :** **For an AHI≥5 :** ***Pooled sensitivity*** **69%** ***Pooled specificity*** **56%** **For an AHI≥15 :** ***Pooled sensitivity*** **79%-82%** ***Pooled specificity*** **50%-62%** **For an AHI≥30 :** ***Pooled sensitivity*** **87%** ***Pooled specificity*** **46%.**		

Abbreviations : AHI: Apnoea hypopnoea index; BQ: Berlin Questionnaire; DOR: diagnostic odds ratio; ESS: Epworth Sleepiness Scale; OSA: Obstructive sleep apnoea; PLMD: Periodic limb movement disorder; PSG: Polysomnography; RBD: REM sleep behaviour disorder; SBQ: STOP-Bang questionnaire.

Table 8. Summary of studies on driving simulators in normal subjects and untreated OSA patients

Author	Design	EBM	Patient population	Simulator type. Test duration	Results	Comments
Normal subjects						
Pizza et al, 2004 (104)	Observational cohort	4	Healthy volunteers (n=10, 5 men) after normal night and night with complete sleep deprivation. Actigraphy and MSLT, EDS assessed as SSS and VAS	Monotonous 30 min driving simulation and divided attention driving task (DADT), 30 min	The standard deviation of lane position, the mean RT, crash frequency and exceeding the speed limit correlated most highly with MSLT.	Driving simulation is suitable to evaluate sleepiness in normal subjects
Contardi et al, 2004 (105)	Observational cohort	4	Healthy subjects (n=10, 5 men). Before each driving task, sleepiness assessed by Stanford	Monotonous 30 min driving simulation task every 2 h	Assessed the circadian variations of alertness in healthy subjects. Driving performances deteriorated or improved according to the circadian variation of alertness.	The standard deviation of lane position, comparing the differences among the 10 min blocks in each task is the parameter most significant for the evaluation of sleepiness in

			Sleepiness Scale (SSS) and Visual Analogue Scale (VAS)			**healthy subjects**
Banks et al, 2005 (106)	**Observational cohort**	**4**	**20 healthy volunteers (9 men), partial sleep deprivation, and partial sleep deprivation plus alcohol.**	**AusEd simulator, 70 min**	**Sleep latency on MWT was a reasonable predictor of simulator performance in sleepy alcohol-impaired normal subjects.**	
Philip et al, 2005 (107)	**Observational cross over**	**4**	**Healthy men (n=12) studied after controlled habitual sleep (8 hours)or restricted sleep (2 hours)**	**Real driving (1200 km) or simulated driving**	**Fatigue can be equally studied in real and simulated environments, but reaction time and self-evaluation of sleepiness are more affected in a simulated environment. Real driving and driving simulators are comparable for measuring line crossings, but the effects are of higher amplitude in the simulated condition.**	**Although not in OSAS, important as comparison between a simulator and real driving**

Hallvig et al, 2013 (108)	**Observational**	**4**	**Normal healthy subjects (n=10, 5 women) studied under both day and night driving conditions**	**High fidelity moving base simulator versus real driving**	**Both for real and simulated driving, the response to night driving was rather similar for subjective sleepiness and sleep physiology. Lateral variability was more responsive to night driving in the simulator, while real driving at night involved a movement to the left in the lane and a reduction of speed, both effects being absent in the simulator. In absolute terms, simulators cause higher sleepiness levels than real driving.**	**Generalisations from simulators to real driving must be made with caution**
Untreated OSA						
Findley et al, 1989 (109)	**Case control**	**4**	**12 untreated severe OSA, 12 controls**	**Steer Clear, 30 min**	**OSA participants hit more obstacles than controls (44±52 vs 9±7). Follow up post-treatment (n=6): improved performance.**	**Short communication**
Findley et al, 1995 (110)	**Case control**	**4**	**62 OSA (53 men); 12 age- and sex-matched controls and 10 age- and sex-matched volunteers, 10 narcolepsy patients. MVA information from legal authorities.**	**Steer Clear, 30 min**	**OSA patients hit more obstacles (4.3 ± 0.6% [SEM]) than subjects without sleep apnoea (1.4 ± 0.3%; $p < 0.05$) and volunteers (1.2 ± 0.3%; $p < 0.05$). In OSA patients MVA rate was:** **- 0.05 accident/driver/5 yr for a normal performance on Steer Clear (n=21);** **- 0.20 accident/driver/5 yr for a poor performance (n=25)** **- 0.38 accident/driver/5 yr for very poor**	**Impaired vigilance as measured by Steer Clear is associated** **with a high MVA rate in OSA patients. Simulator performance correlated with severity of SDB in OSA patients**

					performance (n=21).	
George et al,1996 (111)	**Observational cohort**	**4**	**Twenty-one male OSA patients (age 49.3 ± 12.7 yrs; AHI 73 ±29); 21 age- and sex-matched controls, and 16 narcoleptics (12 males, age: 39.6 ±15.2 yrs). PSG followed by daytime MSLT.**	**Driving simulation, DADT, 20 min before each daytime nap**	**OSA and narcoleptic patients performed worse than controls. Half of either patient group performed as well as controls. Only weak relationship between tracking and MSLT in either group.**	**Degree of impairment difficult to predict from sleepiness alone**
George et al, 1996 (112)	**Case control**	**4**	**21 male OSA patients (same group as in previous article) and 21 age- and sex-matched control subjects. PSG followed by MSLT**	**Driving simulation, DADT, 20 min, before each daytime nap**	**Patients performed much worse than control subjects in all measures, with the largest difference in tracking error (OSA: 228 ± 145 cm, controls: 71 ± 31 cm, $p < 1 \times 10^{-9}$). Half of the patients were worse than any control subject, some showed performance worse than control subjects impaired by alcohol.**	**MSLT and AHI explained less than 25% of the variance in tracking error, making individual prediction problematic.**

Barbe et al, 1998 (43)	**Case control**	**3**	**60 OSAS (AHI 58±3/h) and 60 age- and sex-matched controls**	**Steer Clear, 30 min**	**Patients had more MVA than controls (OR 2.3) and were more likely to have had ≥ 1 accident (OR 5.2). No correlation between the degree of EDS, anxiety, depression, number of respiratory events, nocturnal hypoxemia, level of vigilance, or driving simulator performance and the risk of MVA in OSA patients.**	**Marked as 3 for numerosity of the sample**
Findley et al, 1999 (113)	**Case control**	**4**	**31 patients with untreated OSA (27 men), 16 patients with narcolepsy, and 14 healthy controls**	**Steer Clear, 30 min**	**Patients had more collisions than control subjects at Steer Clear (p=0.006). Inter-subject variability in errors among the narcoleptic patients was four-fold that of OSA patients, and 100-fold that of controls; the variance in errors among untreated OSA patients was 27times that of controls. Differently from control subjects, showed no clear evidence of increasing collision errors with time-on-task (adjusted R^2=0.22), while OSA patients showed a trend toward vigilance decrement (adjusted R^2=0.42, p=0.097), and narcolepsy patients evidenced a robust linear vigilance decrement (adjusted R^2=0.87, p=0.004).**	**The association of disorders of excessive somnolence with escalating time-on-task decrements**

Juniper et al, 2000 (114)	**Case control**	**4**	**OSA patients (n=12, median ODI 41.1/h), controls (n=12, median ODI 0.8/h).**	**Driving simulator and DADT, 3 x 30 min drives with different parts of road ahead visible**	**Patients with OSA performed worse than controls under all three conditions, particularly when vision of the road was limited.OSA patients may be more impaired when road vision is restricted, eg fog**	**Mechanistic study**
Risser et al, 2000 (115)	**Case control**	**4**	**15 OSAS and 15 controls**	**Systems Technology, Inc. DrivingSimulator (STISIM®), 60 min**	**The OSA group had significantly greater variability in lane position, steering rate, and speed than controls. The apnoea group also had more crashes, more numerous and longer EEG attention lapses. Except for speed and steering rate variability, these differences increased over the 60-min task. Measures of lane position variability and crash frequency were positively correlation with attention lapse frequency and duration.**	**Mechanistic study, suggesting that poorer driving performance and crashes are not entirely due to overt sleep, but inattention due to sleepiness.**
Hack et al, 2001 (116)	**Case control**	**4**	**26 OSA patients and 12 controls, experimental conditions: sleep deprivation or**	**Driving simulator and DADT, 90 min**	**Sleep deprived, alcohol and untreated OSA patients performed worse than controls. Performance in untreated OSA between alcohol intoxication and sleep**	**Driving impairment in OSA more compatible with sleep deprivation that impaired motor or**

			alcohol consumption		**deprivation**	**cognitive skills**
Turkington et al, 2001 (117)	**Observational cohort**	**2b**	**150 patients (82% male) referred for sleep studies. Questionnaire about real world driving.**	**Driving simulator and DADT, 20 min**	**Older age, female sex and self-reported alcohol consumption had greatest influence on simulator performance. Number of self-reported near miss accidents was independently associated with poor perfomance. Number of off road events on simulator independently associated with previous MVA. ESS independently associated with falling asleep at the wheel (OR 1.21) and near miss accidents.**	**100% of individuals who did not have an accident could be identified as opposed to only 10% of those who did.**
Mazza et al, 2005 (118)	**Case control**	**4**	**20 OSA patients (AHI 45± 22) and 40 controls. MWT, sustained attention. Three separate test sessions**	**Driving simulator and DADT, 20 min**	**OSA patients performed worse than controls in all tests at all times. Patients had a high number of off road events - (91±71 vs 40±37/h, p=0.01). Nine out of 10 patients with ESS<10 performed worse than controls in at least 1 test.**	**No effect upon real life driving investigated. High number of events on DASS in controls**
Pichel et al, 2006 (119)	**Observational cohort**	**4**	**129 subjects with suspected OSA, confirmed in 77 subjects (AHI≤10/h: 17.2%, AHI between 10**	**Steer Clear, 300 min; and DADT, 20 min**	**Poor tracking error performance was associated with female gender (OR 6.79, 95% CI 1.37-33.65, *P*<0.05), alcohol intake (OR 3.32, 95% CI 1.03-10.63, *P*<0.05), and accidents in the previous year (OR 5.84, 95% CI 1.33-25.68,**	**Performance on driving simulators associated with sleep complaints in OSA patients. Although these measures are not directly associated to MVA, they**

			and 30/h: 26.9%, AHI>30: 55.9%)		***P*<0.05). Poor reaction time was only associated with age (OR 1.12, 95% CI 1.03-1.21, *P*<0.01). When all three performance measures were studied jointly, only reaction time was associated with self-reported dozing while driving (OR 5.39, 95% CI 1.10-26.32, *P*<0.05), and irresistible tendency to fall asleep was associated with poor tracking error (*P*<0.05).**	**are associated to related circumstances, i.e., dozing and falling asleep while driving.**
Desai et al, 2006 (120)	**Cross over observational**	**4**	**13 subjects with mild OSA (mean RDI 12/h) and 16 subjects without OSA. Performance and neurobehavioral testing after a normal night sleep and after a night of supervised sleep deprivation.**	**AusEd, 30 min**	**Clear effects of sleep deprivation and time of day on performance, but no differences between groups. Perception of daytime sleepiness after sleep deprivation was blunted in OSA subjects compared to controls, despite similar performance decrements.**	**Mechanistic**
Sagaspe et al, 2007 (121)	**Observational cohort**	**4**	**30 males untreated OSAS (AHI 43± 24/h). At MWT: 23.3% were sleepy, 43.4% fully**	**Driving simulator and DADT, 60 min**	**Significant effect of MWT group on standard deviation from middle of road. At post-hoc tests, the sleepy group had worse simulator performance than the fully alert group p =0.006. ESS, AHI,**	**Did not compare either MWT or simulator performance with real world driving**

			alert.		arousal index and TST did not predict simulator performance	
Boyle et al, 2008 (122)	Observational cohort	4	24 patients with OSAS (male=12). Mean ESS 11, AHI not reported	SIREN simulator - high fidelity, front and rear views; 60 min	Significant deterioration in vehicle control during microsleeps	Mechanistic study of effect of micro sleeps on driving performance
Pizza et al, 2008 (123)	Observational cohort	4	30 OSAS patients (29 men, AHI 48±23/h), ESS 12.4±4.4, ESS>11 in 56% of the sample	Driving simulator and DADT, 30 min	Subjective and objective sleepiness correlated with driving performance on the simulator. The most significant correlates of sleepiness were: lane position variability and crash data. Driving simulation data significantly different only when patients were classified on the basis of the ESS score. Patients with an AHI > 40 and patients reporting sleepiness while driving in the past year had worse driving performance	Conclusions: driving simulation+DADT is a suitable objective tool to detect sleepiness in OSAS patients.
Tassi et al, 2008 (124)	Case control	4	12 OSAS and 8 healthy controls, 6 driving	Driving simulation with	Compared to controls, OSA patient showed difficulties in speed adjustment and showed a more cautious behaviour	Mechanistic study Poor sleep indices

			sessions during a 24-h period of sustained wakefulness.	**medium traffic density, ie not so monotonous**	**than controls. This was thought to be the result of a bigger effort to stay awake,**	**were correlated to increased theta and beta activities, as well as to more cautious behavior**
Wong et al, 2008 (125)	**Case control**		**Untreated OSA patients (n=8, mean AHI 49.8/h, mean ESS 11.9) and young healthy controls (n=9, AHI 4.5/h, mean ESS 7.3)**	**AusEd, 30 min, and 10-min PVT every 2 h during 40 h of sustained wakefulness**	**Performance and sleepiness worsened over time in both groups. No difference between OSA and controls in any test.**	

Pizza et al, 2009 (126)	**Observational cohort**	**4**	**24 patients with OSAS. MSLT & MWT and driving simulation on 2 different days.**	**STISIM simulator, 30 min**	**Lane position variability and crash occurrence correlated with sleep latency on the MSLT and more significantly on the MWT. Patients reporting EDS or a history of car crashes showed poor performance on the driving simulator.** **Ability of the simulated driving test to detect:** **-sleepy subjects compared with MWT (area under the ROC curve: 0.8 70 for crashes, 0.958 for lane position viability;** **fully alert subjects on the MWT: the majority of the parameters were significant (area under the ROC Curve: 0.9 for crashes, 0.798 for lane position variability.**	**Important study showing relationship between sleepiness and simulator performance in OSA**
Tippin et al, 2009 (127)	**Case control**	**4**	**25 OSA (18 males, AHI 21.2 ± 19.9,ESS 12) and 41 controls (21 males). PSG and MSLT**	**High fidelity simulator, 60 min**	**OSA patients showed reduced vigilance particularly for peripheral targets, and were sleepier at the end of the drive. Sleepiness correlated with worse performance only in OSA patients. No correlation between vigilance performance and ESS, SSS, AHI or mean sleep latency. Hit rate correlated with min SaO2%. Females had worse**	**Mechanistic study. Fatigue related decline in vigilance for peripheral targets predicted by increased sleepiness.**

					performance	
Vakulin et al, 2009 (128)	**Repeated-measures observational study**	**4**	**38 untreated OSAS (28 males, AHI 46.4± 21.7/h, ESS 9.3±5.3) and 20 controls, studied under 3 conditions in random order: unrestricted sleep, sleep restricted to 4 h, and alcohol.**	**AusEd, 90 min**	**In OSA patients, increased steering deviation and significantly greater deterioration over time compared to controls. The effects of sleep restriction and alcohol were approximately 40% greater in patients with OSA. OSA patients crashed more frequently than controls, especially after sleep restriction and alcohol. In OSA patients prolonged eye closure for ≥ 2 s and microsleeps were significant predictors of driving performance. Braking reaction time was slower after sleep restriction than after normal sleep but not after alcohol consumption, without group differences**	**Mechanistic study. No correlation with real life accidents**
Pizza et al, 2011 (129)	**Observational cohort**	**4**	**OSAS patients (n= 43, male, mean AHI 55± 16). PSG and MWT**	**STISIM, 30 min**	**47% had crashed in previous year and considered sleepiness a major factor. Higher ESS associated with earlier crashes on simulator. 65% continued to drive while sleepy. Within this subgroup ("risky behavior"), patients who reported a crash were sleepier according to ESS (MWT p= 0.0682) and crashed more frequently and sooner than those who**	**Poorer simulator performance in patients at risk who continued to drive (advising about driving not an issue in those who have chosen not to drive anyway). Simulators only recommended as a research tool.**

					did not report a crash.	
Filtness et al, 2011 (130)	**Case control**	**4**	**19 CPAP-treated male patients and 20 male controls, normal night's sleep and sleep restriction to 5 hours.**	**Realistic car simulator, 2 hour**	**After a normal night's sleep, patients and controls showed similar driving performance and ability to assess the levels of their own sleepiness, with both groups driving 'safely' for approximately 90 min. After sleep restriction, patients had a significantly shorter (65 min) safe driving time and had to apply more compensatory effort to maintain their alertness compared with controls. They also underestimated the enhanced sleepiness. There were generally close associations between subjective sleepiness, likelihood of a major lane deviation and EEG changes indicative of sleepiness.**	**Mechanistic study. With a normal night's sleep, effectively treated older men with OSA drive as safely as healthy men of the same age. However, after restricted sleep, driving impairment is worse than that of controls.**
Ghosh et al, 2012 (131)	**Observational cohort - derivation and validation of model to protect task failure on simulator**	**2b**	**Exploratory cohort n=72, validation n=133. All with OSAS of sufficient severity to warrant a trial of CPAP. Mean ESS 13, ODI 35.**	**PC based version of a fully immersive simulator**	**32% completed one hour drive without incident, 22% failed, 46% indeterminate. Prediction models using standard deviation of lane position (SDLP)± reaction time at an event could predict those who would fail test (sensitivity 82%, specificity 96%). Results confirmed in validation cohort. Task failure (crash, major driving incident) could be predicted from continuously measured**	**. More credible than other simulators a third of high risk group could complete approx one hour of "motorway driving" without incident. Use of continuous variable useful in that predicts the person who should have failed but "got away with it" and can**

					SDLP, but driving simulator performance did not predict MVA risk in real life.	**be used for repeated testing**
Gieteling et al, 2012 (132)	**Case control**	**4**	**Patients with periodic leg movement disorder (PLMD, n=16), OSAS (n=18, mean AHI 47.9/h) and controls (n=16). 24-h PSG**	**25 minute task. PC version of simulator developed by Brouwer et al (refs 20-21)**	**Decreased performance in patients compared to controls. Trend for worse performance in OSA compared to PLMD patients. Severity of disorder unrelated to performance.**	**At start patients and controls performed similarly, but patient performance decreased clearly with time.**
Philip et al, 2013 (133)	**Case control**	**4**	**19 patients with idiopathic hypersomnolence or narcolepsy, 17 OSA (AHI: 21.5 ± 7.5) and 14 controls. MWT (40 min, 4 times during day)**	**Real car driving simulator, 40 min**	**4 groups based on MWT, pathological (sleep latency 0-19 min), intermediate (20-33 min), alert (34-40 min) and control (>34 min). Patients with pathological sleep latency had significantly more inappropriate line crossings compared to other groups.**	
Vakulin et al, 2014 (134)	**Observational study**		**Untreated OSA patients (n=35) undergoing anthropometric, clinical, and**	**AusEd,90 min**	**Based on steering deviation data collected in 20 normal controls (mean±SD 36.5±9.2 cn), OSA patients were classified as "resilient" drivers (steering deviation<54.6 cm) or**	**The majority of OSA patients (62%) performed well even after sleep deprivation or alcohol.**

			neurobehavioral investigations. Patients studied under 3 conditions in random order: unrestricted sleep, sleep restricted to 4 h, and alcohol.		**“vulnerable” drivers (steering deviation≥54.6 cm, n=15, 38% of the sample). 12 OSA patients experienced at least 1 crash, 11 of them were “vulnerable” drivers. At multivariate analysis, only hours of driving per week (OR 0.69) and the auditory event related potential P2 (OR 1.34) predicted “vulnerable” driver status.**	
Dermidogen et al, 2015 (11)	**Observational cohort**	**4**	**282 commercial drivers Psycho technical assessment system including driving simulation. 30 at high risk for OSA.**	**Simulator not clearly described.**	**47% of the subjects at high risk for OSA failed early reaction time test compared with 28% low risk (p = 0.03). Obese drivers failed the peripheral vision test (p = 0.02). ESS was higher for drivers with history of MVA when compared to those without (p = 0.02). No correlation between ESS and simulator performance.**	**Cognitive psychomotor functions can be impaired in obese subjects and in subjects at high risk for OSA. Such groups should take the battery of tests used in the study**
Vakulin et al, 2016 (135)	**Observational cohort**	**4**	**76 OSAS patients (81% male, AHI 29.8 ± 25.0/h). PSG and quantitative EEG markers**	**AusEd**	**Increased EEG power associated with worse driving performance (steering deviation). No relationships with clinical metrics, eg apnoea index, arousals, oxygen desaturation.**	**Mechanistic study**

May et al, 2016 (136)	**Case control**	**4**	**Community volunteers (=45) in whom screening indicated likely OSA (mean AHI 16.3, mean ESS 8.2). Divided into OSA (> 15 / hr) and normal (<10 per hr and ESS < 10).**	**60 minute motorway . Moderate fidelity simulator – e.g. real car seat, feedback from pedals etc.**	**Performance similar initially but degraded more rapidly in the OSA patients**	**Mechanistic study. Suggests that even in individuals with milder OSA, ie not sufficient to seek medical advice, driving still impaired. 89% of participants did not crash.**
Cross et al, 2017	**Case control**	**4**	**Old subjects with MCI (n=19) and age-matched controls (n=23). Cognitive tests, 10-min PVT, and driving simulation obtained before PSG**	**AusEd,30 min**	**Crashes during driving simulation in 26% of controls and 42% of MCI patients. Poor performance associated with TMT-B in MCI patients only. Similar SDB in both groups, but markers of poor sleep and hypoxemia affected performance only in MCI subjects**	**Both MCI and control groups had no clinical symptoms of SDB.**

Schreier et al, 2017 (137)	**Systematic review**	**1**	**12 studies in sleepy individuals (OSA, narcolepsy or sleep deprived normals) containing both simulated and real driving data were included in the review. Driving simulator most frequently used. Duration generally 20 to 30 min.**	**n/a**	**In general, simulated driving did not reliably predict accidents; especially not on an individual level, despite the modest relationship between simulated and real road test driving performance. Limitations: small sample size, selection, publication and recall bias, "borderline" nature of some driving simulators (eg Steer Clear).**	**The authors concluded that the severity of sleepiness is most likely not the critical factor leading to accidents, but rather the perception of sleepiness and the way that the individual responds to it (the review did not provide any evidence to support this).**

Abbreviations: AHI: Apnoea hypopnoea index; CPAP: continuous positive airway pressure; DADT: divided attention driving task; DASS: divided attention driving simulators; EEG; electroencephalogram; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; MCI: Mild cognitive impairment; MSLT: mean sleep latency test; MVA: motor vehicle accidents; MWT: Maintenance of Wakefulness Test; ODI; oxygen desaturation index; OSA: Obstructive sleep apnoea; OSAS: Obstructive sleep apnoea syndrome; PLMD: Periodic limb movement disorder; PSG: Polysomnography; PVT: Psychomotor vigilance test; RT: response time; RDI: Respiratory Disturbance Index; SDB: Sleep Disorder Breathing; SDLP: standard deviation of lane position; SSS: Stanford Sleepiness Scale; TMT: Trail Making Test Parts; TST: Total sleep time; VAS: Visual analogue scale.

Table 9. Summary of studies on driving simulators in CPAP-treated OSA patients (n=12)

Author	Design	EBM	Patient population	Simulator type. Test duration	Results	Comments
George et al, 1997 (138)	Observational cohort	4	OSA patients (n=17 males, AHI 73.0 ±28.9) restudied 1- 12 months (mean 9.2 ± 4.2) after initiating CPAP.18 age- and sex-matched controls also retested 8.4±3.4 months after initial test. PSG and MSLT	DADT, 20 min	Untreated patients with OSA, who performed much worse than controls in all measures, improved significantly on all measures of performance, particularly in tracking error which rnormalised in all but one patient after CPAP.	Improvement in tracking error was highly correlated with improvement in sleepiness (r = 0.65).
Hack et al, 2000 (139)	RCT	1b	OSA patients (n=59, male, ODI 26 to 35, ESS 15). CPAP or sham for one month cross over.	Very simple graphics DASS, approx 30 min.	Therapeutic CPAP improved SD of steering position and reaction time to target stimuli	Off road events still high (9/hour) after one month therapeutic CPAP. Study shows an important effect of CPAP, but does not address issue of

						simulator as a tool for assessing MVA risk.
Kingshott et al, 2000 (140)	**Observational cohort**	**4**	**OSA patients (n=62) at baseline and after 6 months of CPAP treatment**	**Steer Clear, 30 min**	**Task performance improved with CPAP treatment. AHI was a poor predictor of performance.**	
Munoz et al, 2000 (141)	**Case control**	**2b**	**OSA patients (n=80) before and after 1year CPAP. Controls (n=80)**	**Steer Clear, 30 min**	**Prior to treatment task performance was significantly worse in OSA compared with controls. Performance improved with CPAP.**	
Turkington et al, 2004 (142)	**case control**	**4**	**18 severe OSAS patients before and on days 1, 3 and 7 after starting CPAP, and restudied on days 1, 3 and 7 after CPAP interruption. 18 untreated severe OSAS patients studied on the simulator at the same time points.**	**Driving simulator and DADT, 20 min**	**Performance improved rapidly after CPAP started, and the effect was sustained for up to a week after CPAP withdrawal**	**No effect upon real life driving investigated**

Orth et al, 2005 (143)	**Observational cohort**		**31 patients with OSAS (AHI: 24.8 ± 21.5) before, and after 2 and 42 days of CPAP**	**Tests of vigilance, alertness and divided attention - all important in driving. Tested separately NOT using a simulator**	**Divided attention and alertness improved significantly during CPAP, vigilance remained unchanged. However, accident frequency (before therapy: 2.7±2.0; 2 days after CPAP: 1.5±1.4; 42 days after CPAP: 0.9±1.3) and frequency of concentration faults (before therapy: 12.4±5.1; 2 days after CPAP: 6.5±3.9; 42 days after CPAP: 4.9±3.3) decreased during simulated driving after therapy. No relationship between accident frequency, concentration faults and daytime sleepiness (ESS), and PSG or neuropsychological findings, respectively.**	**Neuropsychiatric tests of 1. vigilance 2. alertness 3. divided attention. Did not use a simulator**
Mazza et al, 2006 (144)	**Case control**	**4**	**Twenty patients with OSAS (18 males) and 20 non-obese and non-snoring control subjects (17). Ten patients restudied after 3 months CPAP**	**Real car - Minotaure - tests ability to respond to an aquatic obstacle. Also DADT, 20 min**	**Much longer reaction times in OSA than in controls, with lengthening of the vehicle stopping distance of 8.8 m at 40 km/hr and twice the number of collisions. No objective sleepiness or selective and sustained attention deficits. Divided attention deficits did not predict real driving impairment. After CPAP treatment, no difference between patients and controls regarding driving and attention performances.**	**Test of reaction time in a real car. Driving simulator performance did not predict what happened in real car.**

Hoekema et al, 2007 (145)	**RCT**	**2b**	**20 OSAS and 16 controls. Short term RCT comparing oral appliance with CPAP**	**DASS, 25 min**	**At baseline, total lapses of attention were greater in patients than controls. No difference after 2 to 3 months oral appliance compared with CPAP.**	
Antonopoulos et al, 2011 (146)	**Meta-analysis to assess the effect of CPAP**	**1**	**Ten studies on real accidents (1221 patients), five studies on near miss accidents (769 patients) and six studies on the performance in driving simulator (110 patients) were included.**	**n/a**	**Significant reduction in real accidents and near miss accidents in CPAP-treated patients. Significant reduction in accident-related events also observed in the driving simulator. NNT equal to five patients, whereas for near miss accidents, the NNT was two patients. For near miss accidents, meta-regression analysis suggested that CPAP seemed more effective in patients reporting higher baseline accident rates.**	**Sizeable protective effect of nCPAP on road traffic accidents, both in real life and virtual environment.**
Vakulin et al, 2011 (147)	**Case control**	**4**	**11 OSAS patients and 9 controls before and after 3 months CPAP**	**AusEd, 90 min**	**Simulator driving parameters of steering deviation, braking reaction time and crashes were measured at baseline and after approximately 3 months. At baseline, OSAS subjects had significantly greater steering deviation compared to controls. Following CPAP, steering deviation improved in OSA group, but no significant changes were observed in controls. Steering deviation in the OSA group after**	**Mechanistic - shows effect of CPAP. No real life correlation**

					CPAP remained higher than in controls	
Filtness et al, 2012 (148)	**Observational cohort**	**4**	**11 long-term CPAP treated patients with OSAS. One night after normal CPAP, one night after no CPAP.**	**Two-hour test on immobile car with full size interactive computer generated road projection. Audible feedback from "rumble" strips.**	**CPAP withdrawal for one night increased sleep disturbance and lead to significantly more instance a shorter safe driving duration and greater subjective sleepiness. This was confirmed by increased EEG beta activity, i.e., more compensatory effort was being applied. There was a highly significant correlation between subjective and EEG measures of sleepiness.**	**Mechanistic study suggesting that compliance every night was crucial for safe driving**
Ghosh et al, 2015 (149)	**Observational cohort**	**4**	**OSAS patients of sufficient severity to warrant a trial of CPAP. Mean ESS 12, ODI 24.**	**PC based version of a fully immersive simulator**	**Trend towards failing the simulator test in patients who had a MVA in real life in the last 3 years (OR 2, p=0.09). Logistic regression analysis showed only admitting to taking a break less than an hour into long drives remained significant, but the predictive power was low (ROC area under the curve 0.59, 95% CI 0.47–0.71).**	

Abbreviations: AHI: Apnoea hypopnoea index; CPAP: continuous positive airway pressure; DADT: divided attention driving task; DASS: divided attention driving simulators; ESS: Epworth Sleepiness Scale; MSLT: mean sleep latency test; MVA: motor vehicle accidents; NNT:

numbers needed to treat; ODI; oxygen desaturation index; OSA: Obstructive sleep apnoea; OSAS: Obstructive sleep apnoea syndrome; PSG: Polysomnography; SD: standard deviation.

Table 10. Meta-analyses on Effectiveness of continuous positive airway pressure (CPAP) treatment in obstructive sleep apnoea (OSA) among commercial and non-commercial motor vehicle drivers							
Author	**Design**	**EBM**	**Objectives and Patient population**	**Results**	**Comments**	**Methodology**	**Observations**
Patil et al, 2019 (150) **Treatment of** **Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy** **of Sleep Medicine Systematic Review, Meta-Analysis, and**	**Systematic Review and Meta-analysis**	**2b, 3b** **Cohort and case-control studies**	**Non-commercial motor vehicle operators.** **Participants had predominantly moderate to severe OSA and were self-reportedly sleepy, ESS or another tool, or datawas not reported.** **10 non-randomised studies with pre- and post-CPAP assessment of**	**A significant risk reduction following treatment [mean crash rate risk ratio of 0.3 (95% CI: 0.2 to 0.4)], which was considered to be clinically significant.**	**The analyses suggest that CPAP use results in a reduction in crash rates in adults with OSA as assessed by both objective MVC data and self-report from questionnaires.**	**PubMed and Embase databases** **October 2013 to February 2018** **RCTs, observational studies,** **adult patients with OSA,** **study sample size ≥10,** **PAP therapy for at least 4 weeks (other PICOs),** **Head-to-head studies of different PAP devices or PAP versus control condition, and** **reporting of at least one**	**No data reported about compliance even some studies had this data** **The quality of evidence for MVC ranged from low to moderatedue to issues of study design ascertainment of the outcome.** **Follow-up varied ranging up to 2 years before enrollment to 6 years after (range 2–6 years) or**

GRADE Assessment.			**MVC by self-report or objective reports.**			**relevant outcome of interest.**	**prospective follow-up after enrollment between 6–12 months.** **Outcome assessment was through self-report, data from transportation offices, or data from auto insurers.**
Tregear et al, 2010 (151) **Continuous Positive Airway Pressure Reduces Risk of Motor Vehicle Crash among Drivers with Obstructive Sleep Apnea: Systematic**	**Systematic Review and Meta-analysis**	**2a, 3a** **Cohort and case-control studies**	**Commercial and non-commercial motor vehicle (CMV) drivers** **The primary objective was to determine whether <u>CPAP use could reduce the risk of motor vehicle crash</u> among drivers**	**A significant risk reduction following treatment (risk ratio = 0.278, 95% CI: 0.22 to 0.35; P < 0.001).** **Daytime sleepiness improves significantly following a single night of**	**Observational studies indicate that CPAP reduces motor vehicle crash risk among drivers with OSA.** **Studies:** **Barbe et al, 2006.** **George et al 2001. Findley et**	**MEDLINE, PubMed (PreMEDLINE), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library** **through May 27, 2009** **- full-length, pub** **- English language** **- unique (not multiply published) data set,**	**No data reported about compliance even some studies had this data** **BIASES** **-different types of crash: any, or only with property damage...** **-self reported data in 7 studies**

Review and Meta-analysis			**with OSA (9 studies, 1.976 pts). A secondary objective involved <u>determining the time on treatment required for CPAP to improve driver safety</u> (6 studies, 205 pts).**	**treatment,** **Simulated driving performance improves significantly within 2 to 7 days of CPAP treatment.**	**al 2000. Hortsmann et al 2000.** **Yamamato et al 2000.** **Scharf et al 1999. Cassel et al 1996. Engelman et al 1996. Kriger et al 1997.**	**- individuals with OSA, or including a separate analysis of those with OSA.** **- ≥ 10 subjects aged ≥ 18 years.** **- actual crash data to measure the risk for crash among individuals receiving CPAP, and the data must have been presented in a manner that allowed calculation of effect-size estimates and confidence intervals.** **- the study must have attempted to determine the duration following initiation of CPAP treatment for individuals with OSA to reach a degree of improvement that would permit safe driving (within 2 weeks following initiation of CPAP).**	**-pretreatment data about the crash were colected retrospectively, post treatment prospectively (they acted different when they were watched Hawthorne effect)** **-exposure (miles driven per unit time) only for 4 studies** **-type of driving (highway, night...)**

Antonopoulos et al, 2011 (146) **Nasal continuous positive airway pressure (nCPAP) treatment for obstructive** **sleep apnea, road traffic accidents and driving simulator performance:** **A meta-analysis**	**Meta-analysis** **15 articles included** **Primary outcomes: real accidents, near miss** **accidents, and accident-related events in the driving simulator**	**2a, 3a**	**Ten studies on real accidents (1.221 patients), five studies on near miss accidents (769** **patients) and six studies on the performance in driving simulator (110 patients) were included.**	**A statistically significant reduction in real accidents and near miss accidents was observed.** **Likewise, a significant reduction in accident-related events was observed in the driving simulator** **It is estimated that for every five patients being treated with nCPAP, one patient avoids a real road traffic accident,** **whereas for every two**	**This meta-analyses demonstrated a sizeable protective effect of nCPAP on road traffic accidents, both in real** **life and virtual environment.** **Studies: Barbe 2007. Cassel 1996. Engleman 1996. Findley 2000. George 2001. Hortsman 2000. Kryeger 1997. Minemura 1993. Suratt 1992. Yamamato 2000** **On driving**	**Medline, Embase, Scopus, Google Scholar, Ovid and** **the Cochrane Library** **randomised and nonrandomised** **studies, editorials, systematic reviews, meta-analyses,** **short papers, case reports, case series, letters to the editor, personal** **views, special communications and unpublished data.** **April 1981** **and July 2010** **1) Study descriptives; namely sample size, time period of road traffic**	**Real and near miss accidents: from 18 studies 7 with compliance (GOOD COMPLIANCE)** **Driving stimulator: from 6 studies, all included duration of CPAP treatment (7-276 days)** **BIASES:** **-noncompliance 9-36% (violation of anonymity)** **-km driven per patient** **-modyfing effects of time upon the efficacy of nCPAP**

				patients being treated with nCPAP one patient avoids a near miss road traffic accident.	**simulator** **Findley 1989** **George 1992** **Hack 2000** **Orth 2005** **Suratt 1992** **Turkington 2004**	**accidents** **monitoring before and after nCPAP treatment,** **2) Demographicvariables; namely age, sex, male to female ratio andanthropometrics such as weight or body mass index (BMI),** **3) Sleepapnoea related variables; namely AHI and respiratory disturbance** **index (RDI), nCPAP usage (number of hours used per night),sleep apnoea diagnostic tools used for patient recruitment andsleepiness scores,** **4) Driving-related variables; namely number ofpatients with real and near miss road traffic accidents,** **5) Drivingsimulator-related variables: number**	

						of accident-related events,tracking error (standard deviation from the center of the road) and **vigilance reaction time, defined as average time needed to respondto visual stimulus for both before and after nCPAP treatment** **6)method used for data collection (self-report, state records orperformance on driving simulator).**	
Sassani et al, 2004 (152) **Reducing Motor-Vehicle Collisions, Costs, and Fatalities by Treating Obstructive**	**Systematic review and meta-analysis**	**2a, 3a** **Six** **articles included in the meta-analysis, ranged from 9 months**	**Annual OSAS-related** **collisions, costs, and fatalities in the United States.** **Cost-benefit** **analysis of treating drivers suffering from**	**Drivers with OSAS perform** **worse on driving simulators, have higher collision ratesthan controls, and have fewer collisions after**	**Annually, a small but significant portion of motor-vehicle collisions,** **costs, and deaths are related to OSAS. With CPAP**	**MEDLINE-PubMed database** **1980 to 2003** **The criteria for inclusion were original research**	**BIASES** **- Clinic population, not general population**

Sleep Apnea Syndrome		**to 5 years** **in duration**	**OSAS with continuous** **positive airway pressure (CPAP).** **6 studies (9 months-5 years) "The pooled OR included more than 1.290 subjects".**	**treatment withCPAP.** **CPAP treatment can annually reduce collision costs by $11.1 billion,** **prevent more than 500,000 collisions, and save nearly 1,000 lives.**	**treatment,** **most of these collisions, costs, and deaths can be prevented.** **Treatment** **of OSAS benefits both the patient and the public.** **Studies included: Findley 1998, Barbe 1998, Teran-Santos 1999, Hortsman 2000, Lioberes 2000, George 2001**	**regarding** **OSAS and collisions, prevalence of OSAS, and management costs** **and patient compliance.**	

Abbreviations: AHI: Apnoea hypopnoea index; BMI: Body mass index; CMV: commercial motor vehicle; CPAP: continuous positive airway pressure ESS: Epworth Sleepiness Scale; MVC: Motor vehicle collisions; OSA: Obstructive sleep apnoea; OSAS: Obstructive sleep apnoea syndrome; RDI: Respiratory Disturbance Index.

Table 11. Studies on impact of continuous positive airway pressure (CPAP) treatment in obstructive sleep apnoea (OSA) among commercial and non-commercial motor vehicle drivers						
Author, year	**Study type (design)**	**Participants (No and characteristics: sex, age, treatments, comorbidity, etc.)**	**Length of follow-up**	**Quality of the study**	**Results (including analysis of cofounders if any)**	**Notes**
Engleman, 1994 (153)	**Randomised, placebo-controlled, cross-over study**	**32 patients (26 men) with OSA: CPAP vs oral placebo.** **Median AHI 28/h (7→129/h), age 49±1.5yrs, BMI 33±1.6kg/m2.**	**4 weeks**	**1b**	**Less daytime sleepiness on CPAP than during placebo (sleep latency 7.2±0.7 vs 6.1±0.7 min, p=0.03).** **Improvements with CPAP in symptoms ratings (2.1±0.2 vs 4.3±0.3, p<0.001), mood (P<0.05 for several measures), cognitive performance with improved vigilance (obstacle hit in steer clear driving test 76±5 vs 81±6, p<0.01), mental flexibility (trail-making B time 66±5 vs 75±5s, p<0.05), and attention (p<0.05).**	**PSG** **Monitored CPAP use** **Low level of CPAP compliance [3.4 (0.4) hours per night]** **MSLT for objective daytime sleepiness**
Hack, 2000 (139)	**Randomised controlled trial**	**Improvement in steering performance using subtherapeutic NCPAP as**	**1 month**	**1b**	**Subtherapeutic NCPAP did not improve overnight >4% SaO_2 dips/h compared with baseline values, had no significant effect on the**	**PSG, MWT** **No data on CPAP**

		a control. **59 men with OSA (ESS of >10** **received therapeutic or subtherapeutic NCPAP (~1 cm H2O) for 1 month. Simulated steering performance. Men aged between 30 and 75 yrs.**			**measures of steering (except for off-road events, p = 0.05), reaction time, or MWT, although it had a significant effect on the subjective ESS (p = 0.001).** **Even for the off-road events, which are due to gross steering errors where the car is already half over the kerb, there is a trend in favor of therapeutic NCPAP.** **Therapeutic NCPAP improves steering performance and reaction time to target stimuli.**	**compliance** **Male**
Phillips, 2013 (154)	**Randomised crossover trial**	**Health effects after 1 month of optimal CPAP and MAD therapy in OSA.** **126 patients,81% male, 50% sleepy based on an ESS greater than 10, 82% with moderate-severe OSA (PSG - AHI 25.6 [SD 12.3]) and 108 completed the trial with both devices.**	**1 month**	**1b**	**Sleepiness, driving simulator performance, and disease-specific quality of life improved on both treatments by similar amounts, although MAD was superior to CPAP for improving four general quality-of-life domains.**	**PSG** **CPAP vs MAD** **Data on compliance (MAD, 6.50 ± 1.3 h per night vs. CPAP, 5.20 ± 2 h per night)**

		Cardiovascular (24-h blood pressure, arterial stiffness), neurobehavioral (subjective sleepiness, driving simulator performance), and quality of life				
Kay, 2013 (155)	**Randomised controlled trial**	**69 newly diagnosed OSA patients (21-64 yrs of age, AHI> 16, PSG), majority males (85.5%), mean AHI at baseline 43.12 ± 26.1** **ESS at baseline 16.8 ± 3 were randomised (1:1) to placebo or armodafinil (150 mg/day) treatment. No significant differences between treatment groups.** **Exclusion: any unstable medical condition, circadian rhythm disorder, RLS, narcolepsy, other significant sleep**	**2+6 weeks**	**1b**	**150 mg armodafinil on simulated driving performance during a 2-week "waiting period" prior to initiation of CPAP,following 6 weeks of CPAP therapy.** **CPAP compliance** **ESS, FOSQ, MOS-CF6** **Armodafinil was found to improve simulated driving performance in OSA patients with EDS prior to initiation of CPAP. Treatment with armodafinil showed no effect on subsequent CPAP compliance.**	**PSG** **Results regarding treatment with armodafinil before CPAP.** **Strong correlations between primary and secondary endpoints and hours of CPAP use**

		disorders, irregular sleep schedules, use of sedating antihistamines, selective serotonin reuptake inhibitors, muscle relaxants or hypnotics, consumption > 600 mg of caffeine per day, alcohol abuse, simulator sickness, and medical conditions or use of medications contraindicated for use of armodafinil.				
Walia, 2019 (156)	**Cross-sectional prospective study**	**2,059 patients with OSA (age 56.0 ± 13.1 yrs, 45.4% female, 76.0% white), questionnaires (Epworth Sleepiness Scale and Patient Health Questionnaire-9)**	**Average follow-up 124.4 ± 67.3 days**	**2b**	**In the entire cohort drowsy driving incidents reduced from 14.2 to 6.9% after PAP therapy (P < .001). In subgroups, drowsy driving incidents reduced from 14% to 5.3% (P < .001) in patients who self-reported adherence to PAP therapy and 14.1% to 5.3% (P < .001) in patients objectively adherent to PAP therapy.** **For each one-point improvement in Epworth Sleepiness Scale score, the odds of drowsy driving decreased by about 14% (odds ratio 0.86, 95% confidence interval 0.82 to 0.90).**	**USA** **<u>Self-reported and objective CPAP use</u>** **No control group.**
Cassel, 1996	**Cohort**	**78 male patients (25-**	**1 year**	**2b**	**AHI pretreatment 34.2±3.1 events/h. AHI at 1**	**Germany**

(157)		**65yrs), drivers, questionnaire (alertness-related problems while driving), 80 min vigilance test, MSLT** **59 patients completed the study** **Exclusion criteria: chronic intake of sedatives, narcolepsy, periodic limb movement, lung diseases, other chronic medical illnesses, known alcohol and drug abuse.**			**year: 3.1±1.3 events/h** **CPAP 8.9±0.26 cmH2O** **The mean annual distance driven by the group was 29,606±2,367 km/year.** **Sleeping spells, fatigue, vigilance test reaction time, daytime sleep latency improved with treatment.** **The accident rate was significantly decreased from 0.8 to 0.15 per 100.000km.**	**Males** **Excluded other causes of sleepiness** **PSG** **Objective CPAP use available for 44 out of the 71 patients (6.1±0.16 h)** **7 from 78 patients (9%) discontinued CPAP**
Krieger, 1997 (158)	**Prospective, multicentre study**	**The effects of CPAP before treatment and after 3,6, 12 months after CPAP. No control group. Questionnaires (also regarding accidents).**	**12 months**	**2b**	**The number of patients having an accident decreased with treatment for real accidents (from 60 to 36; p<O.OI), as well as for near-miss accidents (from 151 to 32; p<0.01). The average number of accidents per patient also decreased, for real accidents (from 1.6± 1.3 to 1.1±0.3; p<0.01) and for near-miss accidents (from 4.5±6.5 to 1.8±1.4; p<0.01). The cost, in**	**PG, PSG** **No control group.** **No difference on CPAP adherence between patients reporting**

		973 patients proposed to CPAP, 893 underwent CPAP, 547 patients completed the study. **Age 56.6±20.7yrs, 86.5% males,** **%), PSG 725, AHI 59.8±25.8/h. PG 168, AHI 34.9±21.1/h.**			**terms of days in hospital related to accidents, decreased from 885 to 84 days.** **Treatment with CPAP decreases the number of accidents occurring in OSA patients.**	**accidents and patients reporting no accidents (5 h 57 min±1 h 53 min vs 6 h 7 min:±:1 h 58 min).**
Scharf, 1999 (159)	**Prospective outcome study**	**Number of automobile accidents and near-miss automobile accidents surveyed by questionnaire.** **316 patientswith diagnosed and treated OSA, 234 men, 82 women** **Mean age, 48.79 +/- 0.67 yrs; mean pretreatment**	**6 months**	**2b**	**Significant decreases were found in the number of incidents of excessive daytime sleepiness, headaches on awakening, physician visits, days absent from work, and automobile accidents or near misses with NCPAP therapy. Patients also reported subjective increases in productivity, quality of life, physical and mental condition, and short-term memory and reduction in both diastolic and systolic blood pressure. Effective treatment of OSA results in improvement both in preexisting symptoms and in quality of life. Improvement in many of the major problems experienced by patients seeking treatment has important implications for preventive medicine**	**PSG** **Surveyed by questionnaire** **Data on CPAP adherence (6.58 ± 0.06)**

		RDI 42.9 +/- 1.7 episodes per hour and 2.8 +/- 0.2 episodes per hour with NCPAP treatment).			**as well as health care cost containment.**	
Yamamoto, 2000 (160)	**Prospective observational study**	**Long-term effects of CPAP via questionnaire before and after nasal CPAP treatment.** **74 male patients (age 49.5 ± 10.8, BMI 29.7± 5.4), severe OSAS, PSG,** **driving history for 2 yr.** **Epworth Sleepiness Scale (ESS),** **mood by the Self-related Depression Scale (SDS).** **47 patients (63%) responded to these questionnaires. 46 of 47 had continued to use the**	**2 yrs (38.8±8.2 months)**	**2b**	**No traffic car accidents were observed among the 39 routine car users during treatment, while 13 of 39 patients (33%) had a car accident before treatment. Although near-miss accidents had been reported by 32 of 39 patients (82%) before treatment, only 4 patients reported near-miss accidents during nasal CPAP treatment. The mean score of ESS was significantly reduced in 46 patients after nasal CPAP. The mean score of SDS was also decreased (P<0.01) after nasal CPAP in 46 patients. Although 26 of 41 patients had been depressive on SDS before treatment, the mood was improved in 13 patients after nasal CPAP.** **These results suggest that long-term nasal CPAP treatment reduces the rate of traffic car accidents and improves the EDS and the mood in patients with OSAS.**	**PSG** **Japanese** **Male** **Mean duration of CPAP was 38.8±8.2 months, CPAP compliance of 97.8%**

		nasal CPAP and completed the questionnaire (mean duration and CPAP level were 38.8±8.2 months, CPAP compliance of 97.8%)				
Orth, 2005 (143)	**Observational prospective study**	**Neuropsychological testing of different attention aspects,** **driving simulation, therapeutic effects of CPAP.** **Driving simulator investigation and neuropsychological testing of alertness, vigilance and divided attention in 31 patients with PSG confirmed OSAS (apnoea–hypopnoea index 24.8±21.5/) before, and 2 and 42 days after**	**42 days**	**2b**	**Significant improvements were seen in terms of alertness and divided attention, whereas vigilance remained unchanged throughout the course of CPAP therapy. However, accident frequency (OSAS before therapy: 2.7±2.0; 2 days after CPAP: 1.5±1.4; 42 days after CPAP: 0.9±1.3) and frequency of concentration faults (OSAS before therapy: 12.4±5.1; 2 days after CPAP: 6.5±3.9; 42 days after CPAP: 4.9±3.3) decreased in the simulated driving situation after 2 and 42 days of therapy. No relation** **between accident frequency, concentration faults and daytime sleepiness.**	**PSG** **Males** **No data on CPAP compliance**

		initiation of CPAP. **31 male patients, 55.3±10.2 yrs; BMI: 29.9±2.2 kg/m2; 24 (77%) agreed to CPAP therapy** **and 21 (68%) completed the study 42 days after initiating CPAP** **Exclusion criteria: cerebral diseases (head injuries, cerebral ischemia and encephalitis); central nervous stimulating or relaxing medication; alcohol or drug abuse; disability to drive a car; chronic obstructive pulmonary disease; and pregnancy.**				
Hui, 2006 (161)	**Large cross-sectional epidemiologic**	**1.016 bus drivers (971 men): 45.3 (7.5) years, BMI 24.9 (3.6) kg/m2, neck circumference 38.9**	**3 months**	**2b**	**BMI, snoring intensity and neck circumference were the positive independent factors associated with the RDI.**	**Only 9 patients with CPAP** **CPAP usage of**

	al study	**(3.1) cm and Epworth sleepiness score 4.8 (4.0).** **Among 211 who underwent home sleep study, 85 (40.3%), 55 (26.1%) and 37 (17.5%) had RDI ≥5, ≥10 and ≥15/h respectively at PSG for confirmation** **Drivers with accidents n=6** **Without accidents n=1.010** **None of the 6 drivers with history of RTA took sedating antihistamines**			**9 accepted CPAP prescription** **after 3 months with CPAP usage of 4.5 (1.3) h/night.** **No significant change in SAQLI, digit symbol, trail A and stroop colour assessment**	**4.5 (1.3) h/night.**
Barbe, 2007 (162)	**Case-control, prospective, controlled study**	**80 patients with OSAS (78 males) vs 80 healthy subjects.**	**2 years before and the 2 years after study entry at**	**2b**	**Automobile collision risk for OSAS RR = 2.57; 95% CI = 1.30–5.05.**	**PSG** **CPAP compliance was evaluated (5.9 8 0.3**

		Excluded: shift workers, drug abusers psychiatric disorders, epilepsy, narcolepsy, RLS. **Patients group: ESS=12±1, age=49±1ys, AHI=60±2/h** **Control group: ESS=3±0.2, age=46±1**	**which CPAP was initiated**		**After CPAP RR = 0.41; 95% CI = 0.21–0.79** **In controls RR = 0.49; 95% CI = 0.17–1.40. The magnitude of this fall between groups was not different (p for interaction = 0.68), even after adjusting for body mass index, alcohol intake and Epworth scale.** **The risk of suffering a traffic collision was significantly reduced after inclusion in the study. Yet, as this reduction also occurred in the control group, this effect may not be due to CPAP therapy.**	**h/night).** **They had exclusion criteria.** **Reduction also occurred in the control group.**
Komada 2009 (39)	**Cross-sectional retrospective study and a prospective long-term follow-up study**	**616 OSAS drivers (age 46.3±10/1yrs, BMI=27.4±4.7kg/m2) vs 600 male controls (age 45.5±9.8/h, BMI 23.4±2.9kg/m2).** **CPAP prescribed for 365 patients with AHI>20/h and 291 patients (76.7%) continued to use CPAP for >5ys**	**72±7.6months**	**2b**	**Mean AHI of 291 patients before CPAP: 61.6±22.8/h.** **Mean duration of CPAP use: 72±7.6 months.** **OR for MVA vs general population=2.36.** **MVA significantly higher in patients with ESS>=11 or AHI>40/h.** **AHI significantly higher in the group with multiple MVA.** **CPAP - effective for reduction of MVA.** **No significant difference between the control group and the CPAP-treated OSAS group at**	**Japanese population** **Males** **PSG: manually scored** **Mean duration of CPAP use: 72±7.6 months**

					follow-up.	
Avlonitou, 2012 (163)	**Prospective study**	**50 patients (41 males)**	**6 months**	**2b**	**CPAP significantly improves SQALI score and ESS (ESS 13.7±6.5/h, at 6 months 3.9±3.8/h, p<0.01), "sleepiness while watching a spectacle" (96%), "reading" (95%), "carrying on a conversation" (95%), "driving" (92.9%), "restless sleep" (87.8%), and "urinating more than once per night" (84.8%)**	**PSG** **Driving was only an improved symptom** **Mean CPAP usage 4.5±0.5/h.**
Alakuijala, 2014 (164)	**Cohort-study**	**34 healthy (23 females) controls** **in order to determine the normative data for Oxford Sleep Resistance Test (OSLER), and for multiple unprepared reaction time (MURT) test.** **Were evaluated modifications in OSLER and MURT values in 192 patients who were referred for suspicion of**	**6 months**	**2b**	**The OSLER error index (the number of all errors divided by the duration of the session in hours) correlated statistically significantly with sleep latency, MURT time, and ESS.** **Strikingly, OSLER SL, the error index, and median reaction time in the MURT test differed statistically significantly between women and men.** **OSLER and MURT were retested in 29 patients within 6 months after initiation of CPAP therapy. These patients worked as professional drivers and they had had daytime somnolence before the treatment. Treatment improved all the sleep study parameters and ESS scores, no significant change in BMI or medication, and**	**PG** **More females** **Some participants were professional drivers** **CPAP use≥ 4 h per night**

		OSA (PG). **Of 173 treated OSA patients, 29 professional drivers were retested within 6 months of treatment** **Excluded: subjects who considered themselves sleepy, did shift work, used any kind of medication or substances that affect the central nervous system, had signs of any sleep disorder, or who reported sleeping poorly the night before the test.**			**OSLER sleep latency from 33 min 4 s to 36 min 48 s, OSLER error index from 66/h to 26/h, and MURT time from 278 ms to 224 ms; all differences statistically significant.**	
Karimi, 2015 (165)	**Clinical sleep laboratory and population-based control**	**1.478 OSA patients vs 21.118 control** **n = 567 with CPAP available data** **70.4% males**	**3.5+/-1 yrs**	**2b**	**MVA risk ratio of 2.45 (p<0.001)** **Driving distance (km/y), ESS≥16, short habitual sleep time (≤5h/night), use of hypnotics were associated with increased risk of MVA (OR 1.2, 2.1, 2.7, 2.1, all p<0.03)**	**Sweden** **PG** **Also includes females** **CPAP use**

		Mean age 53.6±12.8yrs, ESS 10.6±5.2, AHI 17.9±3.2/h			**CPAP use ≥4h/nightwas associated with a reduction of MVA incidence (7.6 to 2.5 accidents/1000 drivers/y)** **The MVA incidence was reduced by 70.0% among patients withhigh CPAP (≥ 4 h/night) compliance, whereas it increased by 54.0% among noncompliant patients (< 4 h/night or off CPAP).** **Untreated OSA increases the risk of MVA and this is influenced by severe daytime sleepiness.** **Apnoea events do not predict MVA risk, but OSA treatment with CPAP leads to considerable risk reduction.**	**<4h/night were classified insufficiently compliant (n=304)**
Bajaj, 2015 (166)	**Cross-sectional prospective study**	**118 subjects (71 males)**	**2-6 months (median 2.5 months)**	**2b**	**OSA and cirrhosis (age 53±5 years)** **Vs 7 OSA patients without cirrhosis (age 52±4 years) who were initiated on CPAP. Patients were re-tested after a median of 2.5 months (2-6 months) post-CPAP.** **Improvement in PSQI, post-simulator sleepiness change and executive function (reduction in ICT lures). There was a significant reduction in lane deviations over time after CPAP compared to pre-CPAP in both cirrhotic and non-cirrhotic patients.**	**PSG** **No data on CPAP compliance**

					CPAP therapy improves executive function and stimulator performance in patients with OSA regardless of cirrhosis.	
Burks, 2016 (167)	**Retrospective Cohort Approach With Case-Control Matching Determines Study Sub-groups.**	**OSA positive n = 1.613** **OSA negative n = 403** **matched to control drivers unlikely to have OSA n = 2.016, 8.9% females** **Treatment adherence: "Full Adherence" (n = 682, 5.7% females), "Partial Adherence" (n = 571, 4.2% females), or "No Adherence" (n = 360, 4.4% females)**		**2b**	**"No Adherence" cases crash rate was fivefold greater (incidence rate ratio = 4.97, 95% confidence interval: 2.09, 10.63) than that of matched controls (0.070 versus 0.014 per 100,000 miles). The crash rate of "Full Adherence" cases was statistically similar to controls (incidence rate ratio = 1.02, 95% confidence interval: 0.48, 2.04; 0.014 per 100,000 miles).**	**PSG, APAP, non-compliant were excluded.** **No data on the duration of CPAP treatment.** **Adherence according to consensus minimum standard of 4 h/night mean APAP use for ≥ 70% of night**
Sergio Garbarino, **2016 (29)**	**Observational prospective study**	**283 male truck drivers of dangerous goods (TDDGs), OSA in 35.7%.** **Mean age 42.3±8.3 years.**	**2ys**	**2b**	**Subjects with severe OSA risk of NMAs: OR=4.745, 95% CI 1.292–17.424, p=0.019.** **After 2 years of CPAP treatment, the rate of NMAs was comparable with drivers without OSA.**	**PSG** **Male** **Truck drivers of dangerous goods** **Mean CPAP use 345.3±31.7 minutes/night,**

						mean percentage of days of CPAP use >4 hours 80.9±9.8
Grote et al. 2018 (168)	**Retrospective study**	**Certification group (n=132): patients with OSA (AHI>15) undergoing the driving license certification process.** **Control group/clinical CPAP group (n=790): patients with moderate-severe OSA.** **Certification/reference group:** **Age 59 ± 12/57 ± 11 yrs** **BMI 30 ± 5/31 ± 5 kg/m2,** **AHI 33 ± 20/36 ± 20 n/h,** **ESS 12 ± 6/11 ± 5** **Annual driving** **distance**	**12 months**	**2b**	**Over-representation of elderly OSA patients in the certificate group.** **Self-assessed improvement in subjective daytime sleepiness (from baseline to follow-up):** **- two times higher in the certification group than in the reference patient group (mean adjusted change in ESS -8.0 (-8.9 – -7.1) versus -4.0 (-4.4 – -3.5)** **(p < 0.001, GLM analysis, n = 343).** **The change in ESS score from baseline was associated with CPAP compliance (hr/day) in the reference patient group (r=-0.25, p = 0.003), but not in the certification group (r = 0.1, p = not significant [NS]).**	**First study to address the clinical practice** **of driving license attestation in patients with OSA and EDS after** **the new EU regulations in 2014.** **Patients attending the fitness to drive procedure showed anideal treatment response: almost completeadherence and eliminationof**

		41,615/18,543km/year **Mean adjusted PAP compliance data (n=124 certificate group. N=651 in clinical CPAP group):** **- 6.0 (5.4–6.6) h/night certification group** **- 3.5 (3.3–3.8) h/night reference cohort** **(n = 726, GLM analysis, p < 0.001).**				**EDS symptoms.** **CPAP compliance data available**
Findley, 1989 (109)	**Case-control study, computer simulator**	**6 subjects (5 men) with untreated, severe apnoea**		**3b**	**The patients with apnoea hit a greater number of road obstacles during their 30-minute simulated drive than did the control subjects (44 ± 52 in patients with apnoea versus 9 ± 7 in control subjects, p < 0.05). Six patients with apnoea hit fewer road obstacles after treatment with CPAP than before treatment (29 ± 19 before CPAP versus 13 ± 8 after CPAP, p < 0.05).**	**No data about the type of sleep study, compliance, CPAP duration or compliance**
Engleman, 1997	**Cohort study**	**99 patients (11 females) with OSA before and after**	**2-70 weeks, median 22**	**3b**	**Auto-reported driving impairment improved**	**PSG**

(169)		**CPAP, questionnaires** **Age 50yrs, ESS pre-CPAP 14, postCPAP 6 (p<0.001)**	**weeks, 6h/night**		**after CPAP**	
George, 1997 (138)	**Prospective case-control study**	**17 men with OSA (49.7+/-11.2 ys), with initial AHI of 73/h (+/-28.9) were restudied after 9.2 months (+/-4.2) of nCPAP** **18 control groupe** **Exclusion criteria: use of sedatives, diagnosis other than OSA, hypothyroidism, AHI<15/h**	**9.2months +/-4.2**	**3b**	**Performance improved with treatment in patients with OSA.** **MSLT improved significantly under CPAP (7.2±7 vs 13.2±6.7min, p<0.001); no difference between control and treated group.**	**PSG** **Sleep latency/MSLT** **Link with drivers: divided attention driving test** **Self reported CPAP use of ≥6/night**
Hakkanen, 1999 (170)	**Randomized case control study**	**10 drivers with OSAS and their matched controls** **9 weeks of CPAP**	**9 weeks**	**3b**	**MWT and a monotonous on-road driving task, eyeblink duration and frequency and speed control - No significant diference between groups in avaerage blink rate, driving performence in terms of maintenance of speed, no significant lane drifting**	**PSG** **Males** **MWT**
Findley, 2000	**Case-control**	**50 patients (43 males)**	**2ys**	**3b**	**OSA patients had a higher automobile crash rate than all drivers in the state of Colorado**	**PSG**

(171)	**study**	**36 (72%, 30 males) reports using CPAP regularly during 2ys (7.2 ±0.3h/night)** **14 patients (13 males) not used CPAP during 2 ys** **Age 56 ± 2ys, AHI 37 ± 3.8/h**			**(0.07 versus 0.01 crash per driver per year, p= 0.02).** **Patients who were treated with nasal CPAP had a lower crash rate than before treatment (0.07 versus 0 crash per driver per year, p , 0.03)** **Drivers with sleep apnoea were reluctant to report their automobile crashes, for the drivers in this study reported only one-third of the crashes in which they were involved.**	**state of Colorado** **No data on CPAP compliance**
Hortsmann, 2000 (42)	**Retrospective case-control**	**156 OSA patients (56.2±12.5ys, 92% males, BMI 26.3±4.7 kg/m2) vs 160 (56.5±10.4yrs, males 90%, BMI 31.7±6.9 kg/m2) age-gender matched control** **Questionnaire study** **Without known neurological illness.** **Severe vehicle accidents with costs above $600 or personal injury were**	**Doesn't mention CPAP duration**	**3b**	**The accident rates in both patients and the control group were greater than the rate of 0.02 "accidents due to sleepiness" per one million km. Patients with AHI >34/h were more often involved in motor vehicle accidents (12 patients = 19% vs. 4 patients = 6%; p<0.05) and had significantly more MVA per one million driven km than those with AHI = 10- 34/h; vs. 1.1; p<0.05.** **nCPAP in 85 OSA patients→ the motor vehicle accident rate dropped from 10.6 to 2.7 per million km (p<0.05).** **Patients with moderate to severe OSA have an up to fifteen-fold risk increase of MVA which**	**PSG** **Patient were compliant to CPAP** **Swiss driving population** **No data on CPAP compliance**

		considered.			can be reduced by adequate treatment.	
Randerath, 2000 (172)	Cohort study	Daytime sleepiness, sustained attention. 125 healthy volunteers, and two groups of 28 OSA patients each. Study A (125 subjects, 108 males), Study B (28 subjects, 26 men), Study C (28 subjects, 27 men): OSA patients underwent one attention test before and one after nCPAP therapy.	2 days of CPAP	3b	Study A: The error rate in volunteers without symptoms of sleep-related breathing disorders (51 persons) was 4.7 +/- 4.3% (number of errors 14.1 +/- 12.9), 95% CI: 1.2 (number of errors 3.6). No dependence of the error rate on age, BMI or sex was found. In persons with a history of apnoeic events (n = 10), the error rate was 10.6 +/- 10.0% (number of errors 31.8 +/- 30), in those with more than two accidents during the last 5 years (n = 4), it was increased to 15.3 +/- 9.7% (number of errors 45.9 +/- 29.1). Study B: Among OSA patients, no significant learning effect was seen, and prolongation of the test duration beyond 30 min had no effect on the test results. Study C: The error rate improved significantly with nCPAP [10.6 +/- 13.5 vs. 6.4 +/- 8.9% (number of errors 31.8 +/- 40. 5 vs. 19.2 +/- 26.7), p < 0.001].	MSTL, MWT No data on CPAP compliance
George, 2001 (173)	Case-control study	Group of patients with OSA before and after treatment with CPAP,compared with a	3 years	3b	Untreated patients with OSA had more MVCs than controls (mean (SD) MVCs/driver/year 0.18 (0.29) v 0.06 (0.17), p<0.001). Following CPAP treatment, the number of	PSG Male/females?

		control group matched for age, sex, and type of driver's license (commercial or noncommercial). 210 patients of mean (SD) age 52 (11) years, BMI 35.5 (10) kg/m2, AHI 54 (29) events/h. MVC records compared for 3 years before and after CPAP therapy. 182 were current users, 27 were non-users (on no other treatment), 5 patients had had surgery, and 6 patients had died.			MVCs/driver/year fell to normal (0.06 (0.17)) while, in controls, the MVC rate was unchanged over time (0.06 (0.17) v 0.07 (0.18), p=NS). Thus, the change in MVCs over time between the groups was very significant (change = –0.12 (95% CI –0.17 to –0.06), p<0.001)). The MVC rate in untreated patients (n=27) remained high over time. Most of the patients with OSA did not have any collisions. Driving exposure was not different following CPAP. Conclusions—The risk of MVCs due to OSA is removed when patients are treated with CPAP. As such, any restrictions on driving because of OSA could be safely removed after treatment.	BMI unchanged Ontario Self reported CPAP use [5.9 (0.6) hours/day]
Turkington, 2004 (142)	Case-control study	18 patients(94% males), 49.9yrs with severe SAHS (RDI > 50 events/h) performed a driving	2 weeks of CPAP and 1 week follow-up	3b	Significant improvements in tracking error (p = 0.004), reaction time (p = 0.036), and the number of off road events per hour (p = 0.032) were seen in the CPAP treated group compared	Known patients with OSAS. Compliance to CPAP evaluated

		simulator test at baseline (before treatment) and at days 1, 3, and 7 of a 2 week CPAP trial period. CPAP was then discontinued and the patients performed three further driving simulator tests after 1, 3, and 7 days. **18 patients, 51.7yr with severe SAHS acted as controls** **No significant differences** **data between patients treated with CPAP and those who acted as controls.**			**with the controls at 7 days.** **There were no changes in driving simulator test results in the control patients over the seven tests, suggesting that any learning effect of repeated tests is minimal.** **Hypersomnolence (Stanford sleepiness scale) significantly improved in the treated patients while on CPAP (median (IQR) 3 (2–4) at baseline v 2 (2–3) at day 3 on CPAP, p=0.004). After discontinuation of CPAP, sleepiness once again deteriorated (3 (2–4) at day 7 of CPAP, p=0.05). There was no significant change in subjective hypersomnolence in the control group over the study period (3 (2–4) at baseline, p=0.65**	**(4.9 (1.5) hours)** **Discontinuation of CPAP**
Mazza, 2006 (144)	**Randomised case-control study**	**20 pts OSAS (18 males and 2 females) 54.1+/-5.9yr, RDI=44.4+/-13/h and 20 non-obese and non-snoring control**	**3 months**	**3b**	**Patients exhibited much longer reaction times than controls, leading to a lengthening of the vehicles stopping distance of 8.8 m at 40 km/h and to twice the number of collisions. Patients did not demonstrate objective sleepiness or**	**PSG** **No data on CPAP compliance**

		subjects (17 males and 3 females) 52.2+/-8.3yr, matched for age, educational level, and number of years of driving included. 10 patients from each group agreed to participate 3 months after CPAP treatment. **Subjects with history of neurological or psychiatric disease, chronic lung disease, uncorrected visual or auditive impairment, chronic sedative intake or alcohol abuse were excluded.** **Parameters: reaction time; distance to stop and number of collisions on the platform; maintenance of**			**selective and sustained attention deficits. Divided attention deficits were found. However, they did not allow the prediction of real driving impairment.** **After CPAP treatment, there was no longer any difference between patients and controls regarding driving and attention performances.**	

		wakefulness; and sustained, selective and divided attention in laboratory. OSLER test, Continuous Performance Test (CPT), Driving Simulator Test.				
Hoekema, 2007 (145)	**Case-control study**	**20 OSAHS (17 males, age 48.7±11.2yrs) patients and 16 control (13 males, age 48.7±10yrs) subjects during a 25-min driving test.** **After randomisation, 10 patients started OA and CPAP therapy.**	**2-3 months**	**3b**	**Total number of lapses of attention during driving significantly higher in OSAHS patients vs control subjects.** **Total number of lapses of attention was significantly decreased in both the OA and CPAP group. When comparing driving performance between the OA and CPAP group, no significant differences were noted.**	**Simulated driving performance** **Comparing driving performance between the OA and CPAP group** **CPAP use evaluated (6.8±0.6h/night)**
Vakulin, 2011 (147)	**Case-control study**	**OSA patients (n=11, males=10, AHI>45/h, PSG), vs control (n=9, males=7).** **Exclusion: professional driver or shift worker; history of driving < 2 y or < 2 h per week; significant**	**3 months**	**3b**	**At baseline, OSA subjects had significantly greater steering deviation compared to controls (mean [95% CI], OSA group, 49.9 cm [43.7 to 56.0 cm] vs control group, 34.9 cm [28.1 to 41.7 cm], p = 0.003). Following ~3 months of CPAP treatment (mean ± SD 6.0 ± 1.4 h/night), steering deviation in OSA subjects improved by an average of 3.1 cm (CI, 1.4 to 4.9), p < 0.001, while no significant steering**	**PSG** **Some neurobehavioral deficits in patients with severe OSA are not fully reversed**

		medical comorbidities, periodic limb movement, past head injury or depression; medications that may influence sleep and daytime behavioral function (e.g., antihistamines, opiates, antidepressants); history of alcohol abuse or current use of recreational drugs. Control subjects were also excluded if they obtained higher than normal scores on sleep quality and daytime drowsiness questionnaires. **Driving simulator performance assessed at base-line and 3 months later, with OSA patients treated with CPAP during the interval.**			**changes were observed in the control group. Despite the improvement, steering deviation in the OSA group remained significantly higher than in controls (OSA group, 46.7 cm [CI, 40.6 to 52.8 cm] vs control group, 36.1 cm [CI, 29.3 to 42.9 cm], p = 0.025).** **While driving simulator performance improved after ~3 months of CPAP treatment with high adherence in patients with severe OSA, performance remained impaired compared to control subjects.**	**by treatment.** **Mean CPAP use (6.0 ± 1.4 h/night),**

Filtnes, 2012 (148)	**Case-control study, follow-up one night without CPAP**	**11 CPAP-treated, 50-75yrs old males, with OSA, completed a 2h afternoon simulated, realistic, monotonous drive in an instrumented car, twice – following one night with CPAP and without CPAP** **Age 65.6±2.3, BMI 33.1±1.8, ESS 5.2±0.7.**	**One night of CPAP**	**3b**	**Withdrawal of CPAP markedly increased sleep disturbance and led to significantly more incidents, a shorter safe driving duration.** **Highly significant correlation between subjective and EEG measures of sleepiness**	**All were men** **One night without CPAP** **No data on CPAP compliance**
Sangal, 2012 (174)	**Case-control study**	**256 adults (87 males, 169 females; 44 retook the tests a month later), 49 evaluated with PSG and MSLT for narcolepsy and 137 OSA patients treated with CPAP.** **114 of 137 (83.2%) subjects were compliant (use ≥ 4 h/night) for ≥ 70% of nights.**	**One month**	**3b**	**Factor analysis revealed 2 factors—general wakefulness inability and fatigue (GWIF), driving wakefulness inability and fatigue (DWIF).** **No significant correlations found in the OSA patients between ESS, SWIFT, GWIF, or DWIF on the one hand, and sleep efficiency.** **SWIFT (r = 0.16, p = 0.006), GWIF (r = 0.15, p = 0.009) and DWIF (r = 0.14, p = 0.023), but not ESS, were significantly correlated with arousal index. ESS (r = 0.14, p = 0.018) and GWIF (r = 0.14, p = 0.022), but not SWIFT or DWIF, were significantly correlated with AHI.** **ESS, SWIFT, GWIF, and DWIF improved with**	**PSG** **CPAP compliance** **83.2% subjects were compliant (use ≥ 4 h/night) for ≥ 70% of nights**

		Test for Sleepiness-Wakefulness Inability and Fatigue (SWIFT) and Epworth Sleepiness Scale (ESS).			**CPAP** **Improvements in SWIFT, GWIF, and DWIF (but not ESS) were significantly correlated with CPAP compliance.**	

Abbreviations: AHI: Apnoea hypopnoea index; APAP: Automatic Positive Airway Pressure; BMI: Body mass index; CI: confidence interval; CPAP: continuous positive airway pressure; CPT: Continuous Performance Test; DADT: divided attention driving task; DWIF: driving wakefulness inability and fatigue; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; GLM: general linear model; GWIF: general wakefulness inability and fatigue ICT: inhibitory control test; MAD: Mandibular Advancement Devices; MOS-CF6: Medical Outcomes Study 6 Item Cognitive Functioning; MSLT: mean sleep latency test; MURT: multiple unprepared reaction time test; MVA: motor vehicle accidents; MVC: motor vehicle collision; MWT: Maintenance of Wakefulness Test; NS: not significant; OA: Oral Appliance; OR: Odds ratio; OSA: Obstructive sleep apnoea; OSAHS: Obstructive sleep apnoea hypopnoea syndrome OSAS: Obstructive sleep apnoea syndrome; OSLER: Oxford Sleep Resistance Test PLMD: Periodic limb movement disorder; PSQI: Pittsburgh Sleep Quality Index; PSG: Polysomnography; RLS: Restless Legs Syndrome; RDI: Respiratory Disturbance Index; SAHS: Sleep Apnea-hypopnea Syndrome; SaO_2: oxygen saturation; SDB: Sleep Disorder Breathing; SDS: Self-related Depression Scale; SL: Sleep latency; TDDGs: truck drivers of dangerous goods.

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