Electronic Supplement:

European Respiratory Society Statement on Sleep Apnoea, Sleepiness and Driving Risk

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, Teran-Santos J, Turino C, McNicholas WT.

Literature Search Criteria and Details of Report Selection for each Section

1) Epidemiology

Results of the literature search

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 e1 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.

2) Predictors of sleepiness in OSA

Results of the literature search

The search criteria for predictors of sleepiness in OSA and obese patients are reported below. The final selection for analysis included 42 papers for sleepiness in OSA (**Table 4, e-supplement**) and 12 papers for sleepiness in obesity (**Table 5**, **e-supplement**).

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])

3) Questionnaires as screening tools for OSA in drivers

Results of the literature search

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.

4)Evaluation of Sleepiness

Results of the literature search

The search terms: “MSLT and sleep apnea and driving” retrieved 13 references (included n=8);“MWT and driving” retrieved 25 references (included n=12); “Sleep apnea and OSLER” retrieved 12 refs (5 included); “Sleep apnea and DADT” retrieved 14 refs (5 included). Some papers examined more than one test, often in association with driving simulation (see next section).

5) **Driving Simulators in the Evaluation of Fitness to Drive**

Results of the literature search

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 e2.** 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 7, e-supplement**). **Table8,**

e-supplement summarises 12 studies on driving performance before and after CPAP treatment.

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

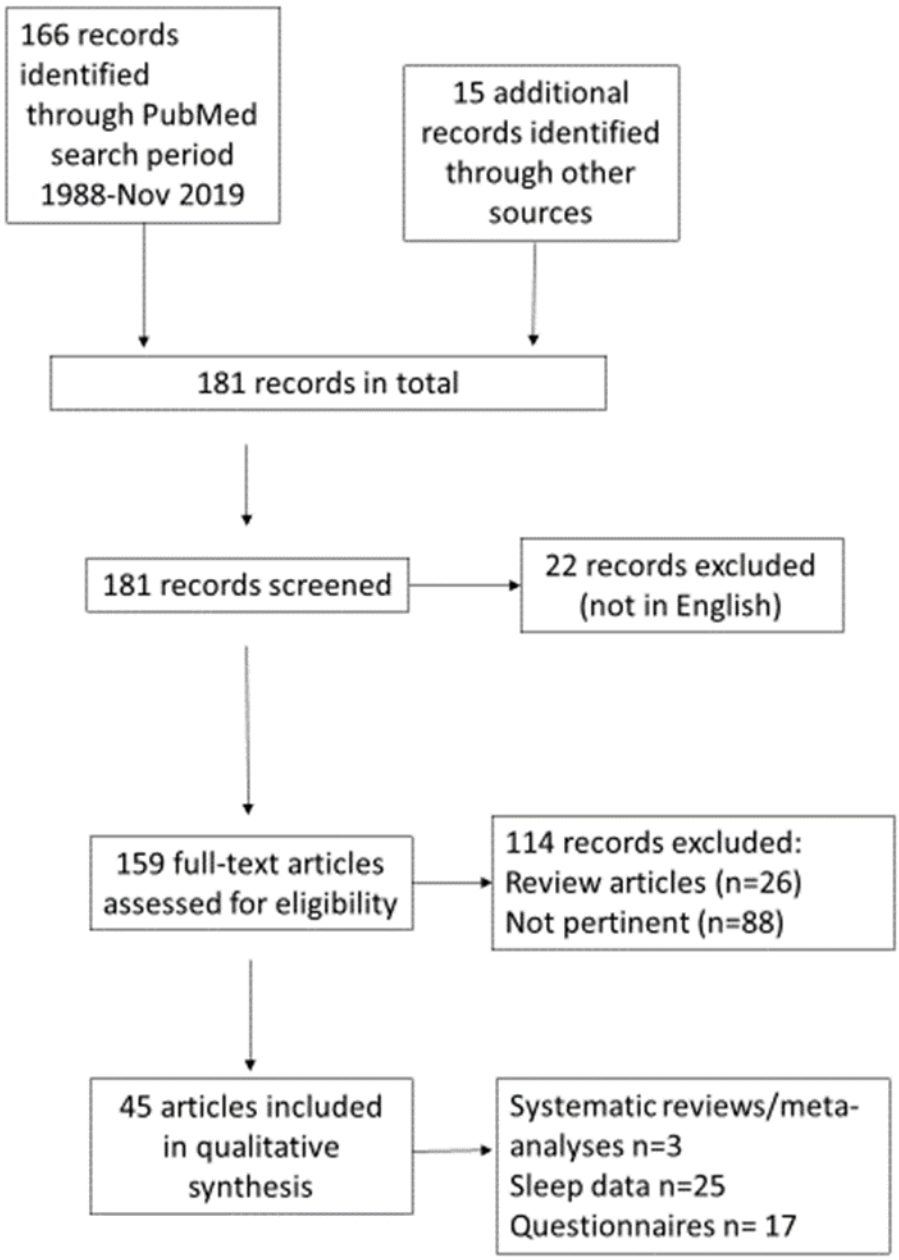
Results of the literature search

The selection process is indicated in Figure e3. 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. From 200 articles considered relevant, 34 were included (**Table 10, e-supplement**) and a further meta-analysis of CPAP efficacy in OSA is given in **Table 9**, **e-supplement**.

Legend to Figure e1.

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

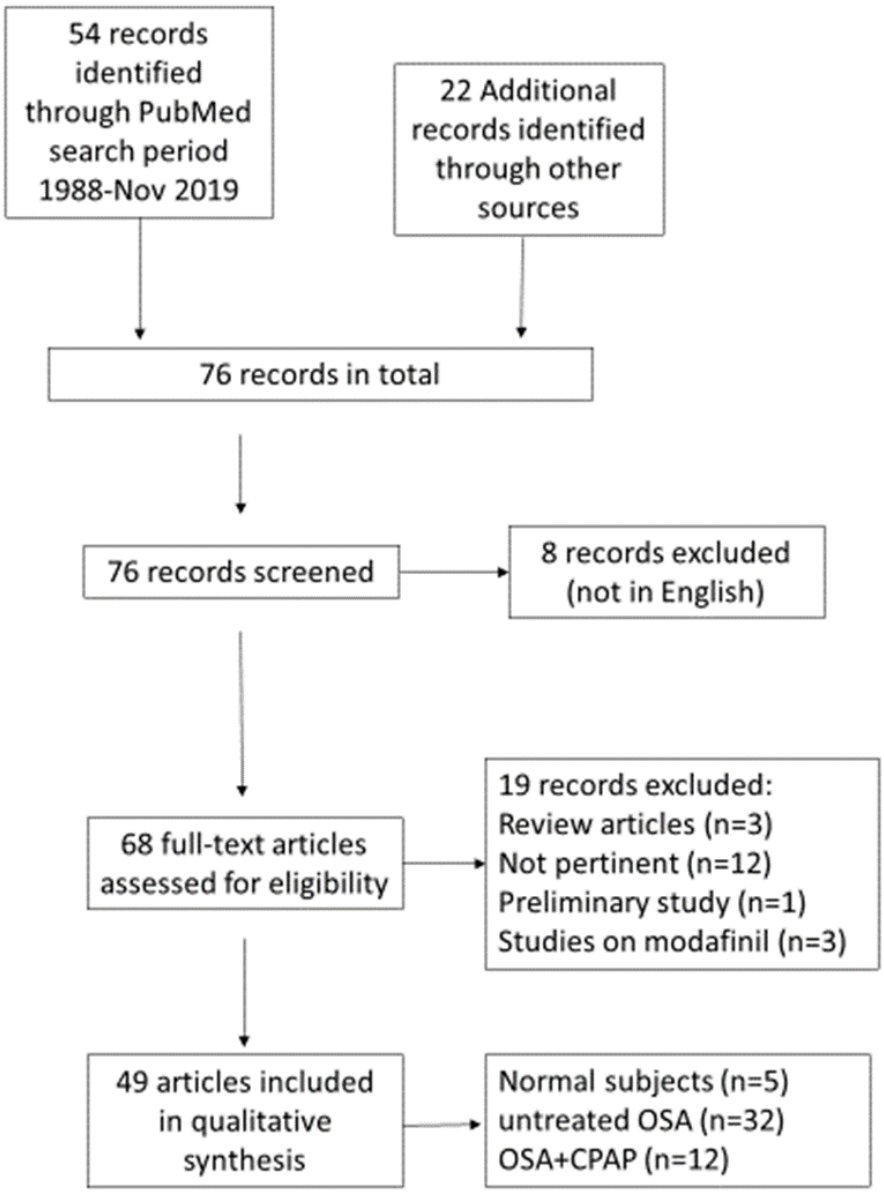
Figure e1.



Legend to Figure e2.

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

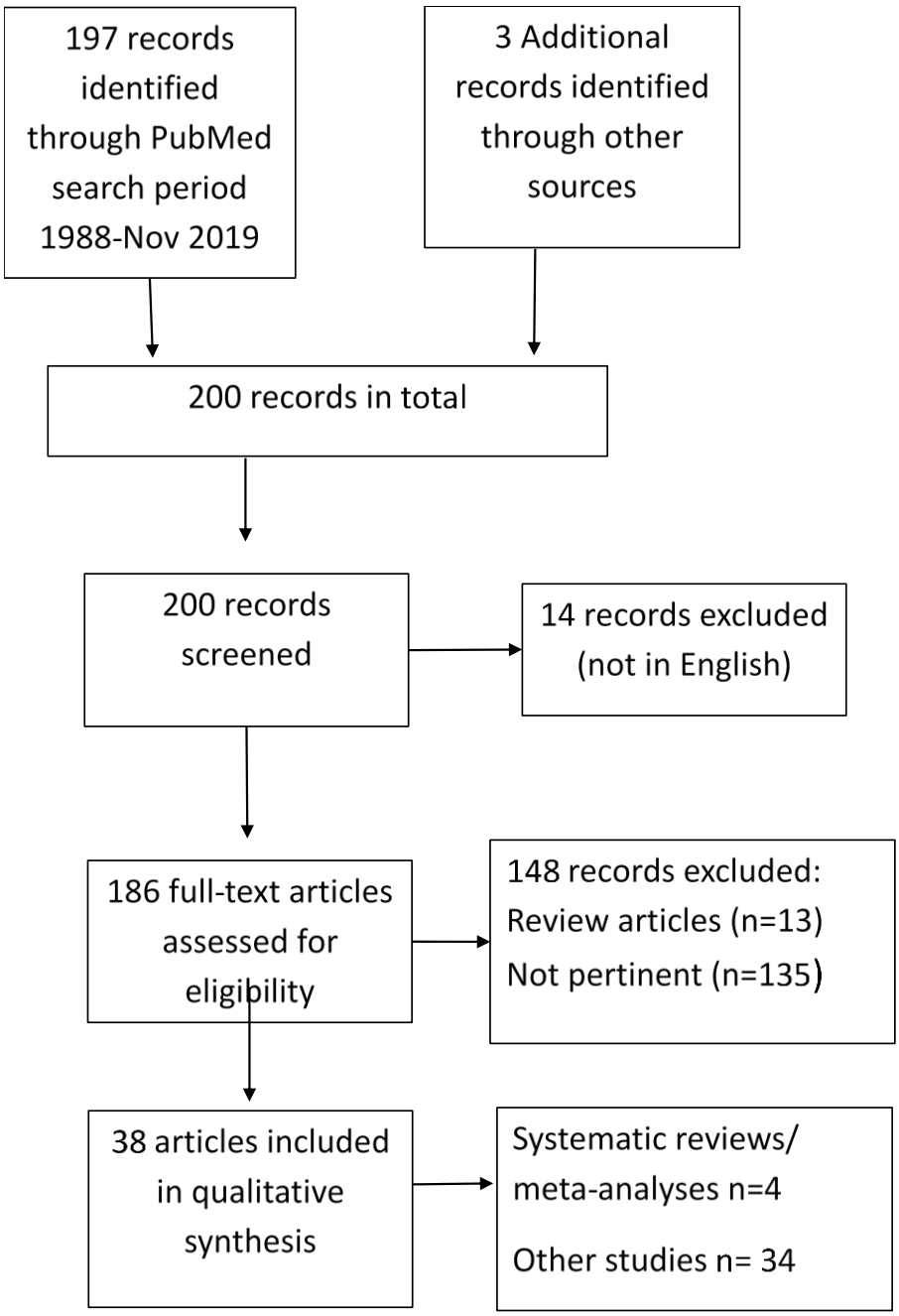
Figure e2.



Legend to Figure e3.

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

Figure e3.



Description of the 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 e1.

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 e2. 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, 2014 (3)	Cross sectional survey	4	3051 drivers. ESS, Basic Nordic Sleep Questionnaire (BNSQ), and a travel questionnaire;	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 sleepiness-related accidents in the past year.	No verification of MVA

			data from the past 24 h and information on usual sleep schedules	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 al, 2008 (6)	cross-sectional survey	4	430 active drivers aged ≥ 70 years. Questionnaires measured self-reported insomnia (ISI), drowsiness (ESS), apnoea risk	One fifth of the cohort had an SACS > 15, indicating high risk for OSAS. Overall driver self-ratings were lower in participants with insomnia symptoms, as well as in those with ESS ≥ 10. Sleep disturbances were not	Participants predominantly male

			(SACS), driving mileage, driver self-ratings (overall and nighttime), and prior adverse driving events	associated with an increase in prior adverse driving events	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 questions including ESS, Berlin Questionnaire (BQ)	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 significant higher on the ESS.	Low response rate Selection bias No verification of

				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.	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: sociodemographic data, personal	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 sleep related).	Likely under-reporting of symptoms. Lower desirable overall rate of

			habits, previous accidents, ESS, and BQ.	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).	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=677, 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 e3. 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 (21)	Prospective observational cohort study	2b	3201 participants (general population) Home polysomnography and	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-reported excessive sleepiness ($p < 0.01$) were each	Self-reported MVA

			questionnaires used to assess history of motor vehicle crashes, usual sleep duration and daytime sleepiness (Epworth Sleepiness Scale)	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,	Cohort study	4	107 sleepy drivers	The frequency of respiratory sleep disorders was	Retrospective MVA

2000 (24)			109 controls matched by age and sex 134 accepted PSG	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).	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 (30)	Case-control	2b	Truck drivers with MVA in last 12 months n=100 Truck drivers without MVA	AHI>17 in 31 cases (49%) and 23 controls (35%) (p=0.12). multivariate analysis OSA was associated with OR for MVA: 3.42 (p=0.01)	Self-reported MVA, no oxymetry data

			n=100 Limited home study in 63 cases and 65 controls		
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 Sweden. Questionnaire and PSG in 161 professional drivers.	No difference between those with and without reported OSAS.Accidents related to sleep debt. Professional drivers had proportionally more sleep debt than non-professionals (p<0.001)	Self-perceived sleep debt more important than OSAS

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 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),	Retrospective, self-reported questionnaires

				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 (41)	Case-control study	3b	189 consecutive patients (sleep clinic population) and a control group (CG) of 40 hospital staff workers matched for age and sex with	122 patients were diagnosed as OSAS and 67 patients as non-apnoeic snorers (NAS). The self-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	Lack of objective data about traffic accidents, no PSG in controls

			the study population Patients underwent a full-night PSG and both patients and the CG completed a questionnaire.	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)	
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	Case-control	3b	Driving records of 29 patients	OSA patients had a 7-fold greater rate of MVA	

al, 1988 (44)	study		with OSA and of 35 subjects without OSA	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 e4. 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	At multivariate analysis, mean sleep latency on MSLT negatively associated with ESS score ≥8 and AHI	EDS assessed in a heterogeneous sample with EDS

			<5 min		
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 stages, respiratory arousal	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	

			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	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]	significant predictors of ESS and 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 with NH>10%	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%		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 e5. 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,	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	

			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)	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 bariatric surgery	4	269 patients (239 females) studied by full PSG, ESS, and FOSQ. EDS defined as ESS ≥10	Average AHI: 29.5±31.5/h, mean ESS score: 6.3±4.8; mean global FOSQ score 100±18. AHI did not correlate with ESS score.	Low self-reported sleepiness
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 e6. 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 OSA,	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.

			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 e7. 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 Sleepiness Scale (SSS) and Visual Analogue Scale	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 healthy subjects

			(VAS)			
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	Generalisations from simulators to real driving must be made with caution

					sleepiness levels than real driving.	
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 performance (n=21).	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
George et al,1996	Observational	4	Twenty-one male OSA patients (age 49.3 ± 12.7 yrs; AHI	Driving simulation, DADT, 20	OSA and narcoleptic patients performed worse than controls. Half of either patient group performed as well as controls. Only	Degree of impairment difficult to predict from

(111)	cohort		73 ±29); 21 age- and sex-matched controls, and 16 narcoleptics (12 males, age: 39.6 ±15.2 yrs). PSG followed by daytime MSLT.	min before each daytime nap	weak relationship between tracking and MSLT in either group.	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	Case	4	31 patients with	Steer	Patients had more collisions than control	The association of disorders

al, 1999 (113)	control		untreated OSA (27 men), 16 patients with narcolepsy, and 14 healthy controls	Clear, 30 min	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).	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 alcohol consumption	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 deprivation	Driving impairment in OSA more compatible with sleep deprivation that impaired motor or 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	100% of individuals who did not have an accident could be identified as opposed to only 10% of those who did.

					asleep at the wheel (OR 1.21) and near miss accidents.	
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 and 30/h: 26.9%, AHI>30: 55.9%)	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, *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).	Performance on driving simulators associated with sleep complaints in OSA patients. Although these measures are not directly associated to MVA, they 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 alert.	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, arousal index and TST did not predict simulator performance	Did not compare either MWT or simulator performance with real world driving
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	Significant deterioration in vehicle control during microsleeps	Mechanistic study of effect of micro sleeps on driving performance

				min		
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 sessions during a 24-h period of sustained wakefulness.	Driving simulation with medium traffic density, ie not so monotonous	Compared to controls, OSA patient showed difficulties in speed adjustment and showed a more cautious behaviour than controls. This was thought to be the result of a bigger effort to stay awake,	Mechanistic study Poor sleep indices 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 performance	Mechanistic study. Fatigue related decline in vigilance for peripheral targets predicted by increased sleepiness.
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	STISIM, 30 min	47% had crashed in previous year and considered sleepiness a major factor. Higher ESS associated with earlier crashes	Poorer simulator performance in patients at risk who continued to drive

			MWT		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 did not report a crash.	(advising about driving not an issue in those who have chosen not to drive anyway). Simulators only recommended as a research tool.
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	2b	Exploratory cohort n=72, validation n=133. All with OSAS of sufficient	PC based version of a fully immersive	32% completed one hour drive without incident, 22% failed, 46% indeterminate. Prediction models using standard deviation of lane position (SDLP)± reaction	. More credible than other simulators a third of high risk group could complete approx one hour of

	validation of model to protect task failure on simulator		severity to warrant a trial of CPAP. Mean ESS 13, ODI 35.	simulator	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 SDLP, but driving simulator performance did not predict MVA risk in real life.	"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 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 neurobehavioral investigations. Patients studied under 3 conditions in random order: unrestricted sleep, sleep restricted to 4 h, and alcohol.	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 “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.	The majority of OSA patients (62%) performed well even after sleep deprivation or alcohol.
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	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”	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

			included in the review. Driving simulator most frequently used. Duration generally 20 to 30 min.		nature of some driving simulators (eg Steer Clear).	(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.

Tablee8.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	Tests of vigilance, alertness and	Divided attention and alertness improved significantly during CPAP, vigilance remained unchanged. However, accident	Neuropsychiatric tests of 1. vigilance 2. alertness 3. divided

			after 2 and 42 days of CPAP	divided attention - all important in driving. Tested separately NOT using a simulator	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.	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 CPAP remained higher than in controls	Mechanistic - shows effect of CPAP. No real life correlation
Filtness et al, 2012 (148)	Observational cohort	4	11 long-term CPAP treated patients with OSAS. One night after normal CPAP, one night	Two-hour test on immobile car with full size interactive	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	Mechanistic study suggesting that compliance every night was crucial for

			after no CPAP.	computer generated road projection. Audible feedback from "rumble" strips.	activity, i.e., more compensatory effort was being applied. There was a highly significant correlation between subjective and EEG measures of sleepiness.	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 e9.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 GRADE Assessment.	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 MVC by self-report or	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 relevant outcome of interest.	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 prospective follow-up after enrollment between 6–12

			objective reports.				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 Review and Meta-analysis	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 with OSA (9 studies, 1.976 pts). A secondary	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 treatment, Simulated driving	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 al 2000. Hortsmann et al	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, - individuals with OSA, or including a separate analysis of those with	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 -pretreatment data about the crash were colected

			objective involved determining the time on treatment required for CPAP to improve driver safety (6 studies, 205 pts).	performance improves significantly within 2 to 7 days of CPAP treatment.	2000. Yamamato et al 2000. Scharf et al 1999. Cassel et al 1996. Engelman et al 1996. Kriger et al 1997.	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).	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)	Meta-analysis	2a, 3a	Ten studies on real accidents (1.221 patients),	A statistically significant reduction in	This meta-analyses demonstrated a	Medline, Embase, Scopus, Google Scholar, Ovid and	Real and near miss accidents: from 18 studies 7 with

Nasal continuous positive airway pressure (nCPAP) treatment for obstructive sleep apnea, road traffic accidents and driving simulator performance: A meta-analysis	15 articles included Primary outcomes: real accidents, near miss accidents, and accident-related events in the driving simulator		five studies on near miss accidents (769 patients) and six studies on the performance in driving simulator (110 patients) were included.	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 patients being treated with nCPAP one	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 simulator Findley 1989 George 1992	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 accidents monitoring before and	compliance (GOOD COMPLIANCE) Driving simulator: from 6 studies, all included duration of CPAP treatment (7-276 days) BIASES: -noncompliance 9-36% (violation of anonymity) -km driven per patient -modifying effects of time upon the efficacy of nCPAP

				patient avoids a near miss road traffic accident.	Hack 2000 Orth 2005 Suratt 1992 Turkington 2004	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) Driving simulator-related variables: number of accident-related events,tracking error	

						(standard deviation from the center of the road) andvigilance 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 ObstructiveSleep Apnea Syndrome	Systematic review and meta-analysis	2a, 3a Six articles included in the meta-analysis, ranged from 9 months to 5 years	Annual OSAS-related collisions, costs, and fatalities in the United States. Cost-benefit analysis of treating drivers suffering from OSAS with continuous positive airway	Drivers with OSAS perform worse on driving simulators, have higher collision ratesthan controls, and have fewer collisions after treatment withCPAP. CPAP treatment	Annually, a small but significant portion of motor-vehicle collisions, costs, and deaths are related to OSAS. With CPAP treatment, most of these	MEDLINE-PubMed database 1980 to 2003 The criteria for inclusion were original research regarding OSAS and collisions, prevalence of OSAS, and	BIASES - Clinic population, not general population

		in duration	pressure (CPAP). 6 studies (9 months-5 years) "The pooled OR included more than 1.290 subjects".	can annually reduce collision costs by $11.1 billion, prevent more than 500,000 collisions, and save nearly 1,000 lives.	collisions, costs, and deaths can be prevented. Treatmentof OSAS benefits both thepatient and the public. Studies included: Findley 1998, Barbe 1998, Teran-Santos 1999, Hortsman 2000, Lioberes 2000, George 2001	management costsand 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 e10. 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,	Length of follow-up	Quality of the	Results (including analysis of cofounders if any)	Notes

		etc.)		study		
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 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	1 month	1b	Subtherapeutic NCPAP did not improve overnight >4% SaO_2 dips/h compared with baseline values, had no significant effect on the 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	PSG, MWT No data on CPAP compliance Male

		between 30 and 75 yrs.			performance and reaction time to target stimuli.	
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. Cardiovascular (24-h blood pressure, arterial stiffness), neurobehavioral (subjective sleepiness, driving simulator performance), and quality of life	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)
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	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	PSG Results regarding treatment with armodafinil before CPAP. Strong correlations

		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 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.			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.	between primary and secondary endpoints and hours of CPAP use
Walia, 2019 (156)	Cross-sectional prospective	2,059 patients with OSA (age 56.0 ± 13.1 yrs, 45.4%	Average follow-up	2b	In the entire cohort drowsy driving incidents reduced from 14.2 to 6.9% after PAP therapy (P	USA Self-reported and

	study	female, 76.0% white), questionnaires (Epworth Sleepiness Scale and Patient Health Questionnaire-9)	124.4 ± 67.3 days		< .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).	<u>objective CPAP use</u> No control group.
Cassel, 1996 (157)	Cohort	78 male patients (25-65yrs), 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.	1 year	2b	AHI pretreatment 34.2±3.1 events/h. AHI at 1 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.	Germany Males Excluded other causes of sleepiness PSG Objective CPAPuse 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). 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.	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 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.	PG, PSG No control group. No difference on CPAP adherence between patients reporting 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.	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	PSG Surveyed by questionnaire

		316 patientswith diagnosed and treated OSA, 234 men, 82 women Mean age, 48.79 +/- 0.67 yrs; mean pretreatment RDI 42.9 +/- 1.7 episodes per hour and 2.8 +/- 0.2 episodes per hour with NCPAP treatment).			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 as well as health care cost containment.	Data on CPAP adherence (6.58 ± 0.06)
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	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	PSG Japanese Male Mean duration of CPAP was38.8±8.2 months, CPAP compliance of 97.8%

		questionnaires. 46 of 47 had continued to use the nasal CPAP and completed the questionnaire (mean duration and CPAP level were 38.8±8.2 months, CPAP compliance of 97.8%)			patients with OSAS.	
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	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

		and 42 days after 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 epidemiological study	1.016 bus drivers (971 men): 45.3 (7.5) years, BMI 24.9 (3.6) kg/m2, neck circumference 38.9 (3.1) cm and Epworth	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 4.5 (1.3) h/night.

		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	
Barbe, 2007 (162)	Case-control, prospective, controlled study	80 patients with OSAS (78 males) vs 80 healthy subjects. Excluded: shift workers, drug abusers psychiatric disorders, epilepsy, narcolepsy, RLS. Patients group: ESS=12±1,	2 years before and the 2 years after study entry at which CPAP was initiated	2b	Automobile collision risk for OSAS RR = 2.57; 95% CI = 1.30–5.05. 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	PSG CPAP compliance was evaluated (5.9 8 0.3 h/night). They had exclusion criteria. Reduction also

		age=49±1ys, AHI=60±2/h Control group: ESS=3±0.2, age=46±1			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.	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 follow-up.	Japanese population Males PSG: manually scored Mean duration of CPAP use: 72±7.6 months
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"	PSG Driving was only an improved symptom

					(87.8%), and "urinating more than once per night" (84.8%)	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 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,	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 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.	PG More females Some participants were professional drivers CPAP use≥ 4 h per night

		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.				
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 Mean age 53.6±12.8yrs, ESS 10.6±5.2, AHI 17.9±3.2/h	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 wereassociated with increased risk of MVA (OR 1.2, 2.1, 2.7, 2.1, all p<0.03) 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	Sweden PG Also includes females CPAP use <4h/night were classified insufficiently compliant (n=304)

					reduction.	
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. CPAP therapy improves executive function and stimulator performance in patients with OSA regardless of cirrhosis.	PSG No data on CPAP compliance
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%		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

		females), or "No Adherence" (n = 360, 4.4% females)				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-	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 –	First study to address the clinical practice of driving license attestation in patients with OSA and EDS after the new EU

		severe OSA. Certification/reference group: Age 59 ± 12/57 ± 11 yrsBMI 30 ± 5/31 ± 5 kg/m^2, AHI 33 ± 20/36 ± 20 n/h, ESS 12 ± 6/11 ± 5 Annual driving distance 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).			-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]).	regulations in 2014. Patients attending the fitness to drive procedure showed anideal treatment response: almost completeadherence and eliminationof EDS symptoms. CPAP compliance data available
Findley, 1989	Case-control study,	6 subjects (5 men) with		3b	The patients with apnoea hit a greater number of road obstacles during their 30-minute	No data about the type of sleep

(109)	computer simulator	untreated, severe apnoea			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, $p < 0.05$).	study, compliance, CPAP duration or compliance
Engleman, 1997 (169)	Cohort study	99 patients (11 females) with OSA before and after CPAP, questionnaires Age 50yrs, ESS pre-CPAP 14, postCPAP 6 (p<0.001)	2-70 weeks, median 22 weeks, 6h/night	3b	Auto-reported driving impairment improved after CPAP	PSG
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 groupExclusion 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	PSG Males MWT

					performence in terms of maintenance of speed, no significant lane drifting	
Findley, 2000 (171)	Case-control study	50 patients (43 males) 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	2ys	3b	OSA patients had a higher automobile crash rate than all drivers in the state of Colorado (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.	PSG 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	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).	PSG Patient were compliant to CPAP Swiss driving population No data on CPAP compliance

		with costs above $600 or personal injury were considered.			Patients with moderate to severe OSA have an up to fifteen-fold risk increase of MVA which 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 control group matched for	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 MVCs/driver/year fell to normal (0.06 (0.17)) while, in controls, the	PSG Male/females?

		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.			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 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	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 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.	Known patients with OSAS. Compliance to CPAP evaluated(4.9 (1.5) hours) Discontinuation

		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.			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	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 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	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 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	PSG No data on CPAP compliance

		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 wakefulness; and sustained, selective and divided attention in laboratory. OSLER test, Continuous Performance Test (CPT), Driving Simulator Test.			difference between patients and controls regarding driving and attention performances.	
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	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	Simulated driving performance Comparing driving performance

		test.After randomisation, 10 patients started OA and CPAP therapy.			group. When comparing driving performance between the OA and CPAP group, no significant differences were noted.	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 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	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 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.	PSG Some neurobehavioral deficits in patients with severe OSA are not fully reversed by treatment. Mean CPAP use (6.0 ± 1.4 h/night),

		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.				
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	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	PSG CPAP compliance 83.2% subjectswere compliant (use ≥

		with CPAP. 114 of 137 (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).			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 CPAP Improvements in SWIFT, GWIF, and DWIF (but not ESS) were significantly correlated with CPAP compliance.	4 h/night) for ≥ 70% of nights

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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