Sleep and Breathing (2020) 24:37–47
https://doi.org/10.1007/s11325-019-01903-6

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Excessive daytime sleepiness in obstructive sleep apnea: implications for driving licenses

Sergio Garbarino[1]

Received: 4 February 2019 / Revised: 14 July 2019 / Accepted: 16 July 2019 / Published online: 24 July 2019

Abstract

Purpose Excessive daytime sleepiness (EDS) while driving is a major international public health issue resulting in a more than doubled risk of motor vehicle accidents (MVAs). Obstructive sleep apnea (OSA) is the most frequent medical cause of EDS. Therefore, the European Union Directive 2014/85/EU determined that "untreated moderate to severe OSA coincident with EDS constitutes a medical disorder leading to unfitness to drive." The paper aims are to provide a brief review of sleepiness and its implications for driving safety, as well as to describe the subjective and objective methods to accurately evaluate EDS in order to assess fitness to drive in patients with OSA.

Methods We examined databases including PubMed, Medline, and EMBASE using the search terms "sleepiness at the wheel, excessive daytime sleepiness, sleepiness measure, sleep-wake cycle, obstructive sleep apnea, driving license, fitness to drive."

Results Significant interindividual variability in EDS exists in patients with comparable severity of OSA. Objective methods of measuring EDS are too expensive and time consuming to be suitable for the certification of driving licenses. The reliability of subjective methods depends upon the clinical setting and subjective tools assess only limited aspects of EDS. Objective measures, such as biochemical biomarkers, must, therefore, support subjective methods.

Conclusions Extensive data have supported different subjective and objective methods for the appraisal of EDS in patients with OSA depending upon the clinical and experimental setting. Challenges remain to determine an appropriate tool for the evaluation of fitness to drive.

Keywords Obstructive sleep apnea · Excessive daytime sleepiness · Driving license · Medical assessment · Fitness to drive

Introduction

Sleepiness while driving is a major international public health issue. Sleepiness has a relevant impact on road safety, as it substantially contributes to the burden of road-related morbidity and mortality [1–5]. The risk of road death is more than three times higher in low-income countries than in high-income countries, with an average rate of 27.5 deaths per 100,000 population and 8.3 deaths per 100,000 population, respectively. Road injuries are the eighth cause of death for all age groups and are the most important cause of death for children and young adults aged 5–29 years [6]. Road crashes cost most countries 3% of their gross domestic product [7]. A recent European survey about sleepiness while driving reported a 17% prevalence of sleepiness episodes during driving [8]. Over the last two decades, studies have estimated the rate of sleep-related road accidents from 3, 10, 20–22 to 33% according to studies conducted in the USA [9], France [10], UK [11], Italy [12], and New Zealand [4].

A recent meta-analysis showed a strong association between sleepiness while driving and motor vehicle accidents (MVAs). Of the 17 studies included, all but one found that a higher risk of MVAs for drivers reporting sleepiness while driving compared to other drivers. The pooled risk estimate for MVAs due to sleepiness while driving was more than doubled [13]. Sleep-related accidents have multifactorial causes and can be erroneously attributed to other causes such as drug or alcohol consumption, inattention, fatigue, decreased energy, speed, and adverse weather conditions [14, 15].

Sleep deprivation, mainly caused by prolonged wakefulness, shift work, or poor sleep quality, is the most frequent

This article is part of the Topical Collection on *Excessive Daytime Sleepiness*

✉ Sergio Garbarino
sgarbarino.neuro@gmail.com

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal/Child Sciences (DINOGMI), Polyclinic Hospital San Martino IRCCS, University of Genoa, Genoa, Italy

cause of sleepiness. Furthermore, somatic diseases and mental disorders can induce sleepiness. Obstructive sleep apnea syndrome (OSA) should receive close attention, given an estimated prevalence of 23.4% among women and 49.7% among men older than 40 years old [16]. Patients with OSA experience a significantly higher risk of accidents with worse personal injuries [17, 18]. Calculated with the population attributable fraction (PAF), the overall risk for MVAs OSA-related in a general population of male drivers is about 7% [19]. This risk can dramatically decrease with medical treatments with sleep hygiene or continuous positive airway pressure (CPAP) for OSA and changes in behavior. Sleepiness-related MVAs are potentially preventable [18, 20, 21].

The European Union Directive 2014/85/EU [22] included OSA among the clinical conditions of Annex III and established new driver licensing regulatory requirements for patients with OSA. Not treated moderate to severe OSA associated with excessive daytime sleepiness (EDS) represents a medical condition leading to unfitness to drive [23, 24].

The scrupulous evaluation of EDS is a pressing social and medical need for professional and non-professional drivers. Agreement on how to assess EDS in patients with OSA is lacking, and the clinical tools to assess it are not sufficient. This paper provides a brief descriptive review of sleepiness and its implications for safety. It describes the available methods to evaluate EDS in a clinical and non-clinical setting to appraise the fitness to drive in patients with OSA following the introduction of Directive 2014/85/EU in Europe.

Materials and methods

The scholarly literature was examined from inception to the present utilizing PubMed, Medline, and EMBASE. Search terms comprised sleepiness at the wheel, excessive daytime sleepiness, sleepiness measures, sleep-wake cycle, obstructive sleep apnea, driving license, and fitness to drive. The authors also consulted the Legal references for European judicial decisions.

Sleepiness and excessive daytime sleepiness

Sleep is a ubiquitous biological imperative that seems to linger evolutionarily across species [25]. High levels of attention and cognitive performance require both that sleep has sufficient duration, continuity, and intensity, and that has not circadian perturbation. Good quality and quantity of sleep are mandatory to prevent individuals from experiencing physiological changes that may predispose to adverse health outcomes [26, 27]. A lifestyle of chronic partial sleep loss may be partly explained by the fact that individuals frequently carry out other activities (work and free time) sacrificing timing and duration of sleep [28]. In late chronotypes, the restraints of early work schedules lead to an increasing sleep debt during the week that diminishes in the weekends. Many people move their sleep and activity times noticeably between the work week and the weekend or other free days; a circadian schedule referred to as "social jetlag" [29]. In our day, sleep deprivation is the most frequent cause of sleepiness and is linked to adverse cardiometabolic outcomes [30, 31].

Some of the deleterious effects of sleep deprivation are due to the disruption of the synergy between homeostatic process depending on sleep and wake (Process S) and the circadian process (Process C) controlled by the circadian pacemaker. Process S increases during wakefulness and declines during sleep, within a value range that changes with a periodicity that is usually trapped to day and night by the Process C. When S reaches the range's lower boundary, it triggers awakening, while close to the upper boundary it triggers sleep [32]. Internal and external stimulation of various kinds (proprioceptive, exteroceptive, enteroceptive, cognitive, and emotional) can contribute to initiating and maintaining waking state [33, 34]. These stimuli induce impulses which travel along the central nervous system to activate the ascending arousal system (AAS), composed of several brain structures within the brainstem and cerebral hemispheres as the thalamus, hypothalamus, and basal forebrain. AAS releases multiple neurotransmitters (monoaminergic and cholinergic) co-driving wakefulness [35] and promoting arousal within the thalamus and cerebral cortex [36]. One proposed term for this arousal drive is Process A since it is driven by the afferent nervous system [33]. Since this process includes emotional and cognitive inputs [34] as well as sensory inputs and is also mostly voluntary, the term psycho-sensory (PS) was proposed [36]. Unlike the input to the C wake drive, input to the PS wake drive can be both voluntary and reactive to its surroundings. The PS output is transient and cannot be predictable. Given the complex regulation of this triple-drive model (Processes C, S, and PS) for sleep and wake, it is not hard to regard sleepiness as a complex, multifactorial, and multi-dimensional condition.

Sleepiness appears to be characterized by subjective feelings and self-perceptions that encompass different situations, with various degrees of sleep propensity, alertness, or vigilance (i.e., the capacity to remain awake together with an adequate, sustained, and selective attention over prolonged periods) affecting human performance [37–40].

Whereas sleepiness is a physiological condition, resulting from the non-linear interplay between triple-drive model [41], EDS represents a pathological condition characterized by an abnormally increased likelihood of falling asleep or lapsing into drowsiness when sleep is not sought or desired. The American Academy of Sleep Medicine (AASM) defines EDS as "the inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily for at least three months" [42]. EDS represents a severe, pathological, disabling condition with essential effects related to gender, age, and comorbidities, such as depression and other disorders commonly linked with fatigue. Fatigue is, however, a different concept which should not be confused with sleepiness [43]. Epidemiological studies of EDS are complicated by varying definitions and by the use of a broad array of subjective and objective instruments. Prevalence rates of EDS consequently range from 4 to 21%, depending on the definition and the method of appraisal [44]. The National Sleep Foundation has performed several population-based surveys, according to which about 30% of respondents suffer from EDS that interferes with quality of life [45]. Severe EDS affects behavioral, physiological, and cognitive operating, as well as the quality of life. EDS results in a reduction of reaction time, vigilance, alertness, and concentration, and impairs the ability to sustain attention-based activities [46]. Sleep loss enhances emotional susceptibility and tolerance to pleasant stimuli and also impairs prefrontal cortical functioning and connectivity involved in inhibitory control [47]. Furthermore, significant sleep deprivation increases sensitivity to rewards and risk-taking [48]; sleep loss can also increase risk-taking behavior. Sleepiness uniquely predicts risk-taking, following the adjustment for the influence of recent sleep, chronotype, chronic sleepiness, and trait sensation seeking [49].

EDS and OSA

The most common medical cause of EDS is OSA. OSA is a widespread breathing disorder related to sleep, which is characterized by repetitive, partial (hypopnea) or complete (apnea) episodes of pharyngeal and upper way collapse, resulting in weak gaseous exchange, oxygen desaturation, and bouts of concomitant hypoxia and hypercapnia. Anatomical factors determining upper airway narrowing together with physiological, non-anatomic factors contribute to cause apnea [50, 51]. The clinical manifestations of OSA differ considerably among individuals. Clustering of symptoms and comorbidities such as arterial hypertension, cerebral-cardio-metabolic complications, neurocognitive disorders, or severe obesity allows discrimination between clinical phenotypes [52, 53].

EDS is a distinctive feature of clinically significant OSA. EDS leads to impaired function, primarily executive functions, reduced quality of life, and poorer cardiovascular outcomes [54–57]. OSA imposes a considerable clinical and epidemiological burden [16]. However, despite its importance, OSA still represents a relatively overlooked and undiagnosed public health condition [58, 59].

Significant interindividual variability in EDS and personal susceptibility to the systemic effects of OSA exist in subjects with comparable severity of OSA, and reasons for this variability remain slightly understood [60, 61]. Measures of OSA severity, including apnea-hypopnoea index (AHI), scarcely correlate with subjective and objective EDS [62–66]. The explanation for this inconsistency may be the individual susceptibility differences in pathogenicity of main underlying mechanisms of OSA, such as intermittent hypoxia, intrathoracic pressure swings, variations in sympathetic and muscular tone, and hemodynamic instability [43].

Positive predicting factors of EDS in OSA comprise African-American race, younger age, obesity, higher sleep efficiency, short sleep duration, increase in respiratory arousals, and nocturnal hypoxemia with activation of the sympathetic nervous system [53, 67, 68] and inflammatory cytokines [69–72]. The correlation of chronotype with OSA is unclear and conditioned by obesity and mood, even if morning chronotype seems to have a protective effect on EDS in OSA [62]. In OSA, sleep deprivation enhances oxidative stress, inflammation, and risk for hypertension [73, 74].

If not properly treated, patients with OSA are at higher risk of experiencing MVAs [8, 12, 75]. However, successful treatment of OSA can re-establish fitness to drive along with its consequent EDS [23]. It is substantial that sleep specialists experienced in the management of OSA and EDS evaluate the effectiveness of treatment [24]. OSA intensity and reduction of EDS require careful consideration before attesting the fitness to drive. Currently, there are only few published national guidelines and evidence-based protocols informing and steering the procedure [76]. Residual EDS in patients successfully treated for OSA may still lead to a significant socioeconomic burden, including road and work-related accidents, reduced quality of life and overall health, neurocognitive impairment, as well as all-cause and cardiovascular morbidity and mortality [77].

Assessing EDS for fitness to drive in patients with OSA

Epidemiological studies on EDS are hampered by the varying definitions of the condition and the variety of subjective and objective instruments used to measure EDS. Consequently, the classification of sleepy subjects with OSA remains a controversial issue. An agreement on how to assess EDS in patients with OSA is lacking. Clinical tools for appraisal of EDS are insufficient, particularly regarding the assessment of fitness to drive.

Subjective measures

Various psychometric tools exist to measure EDS quantitatively [78]. Subjective measures are a fast and cost-effective way of estimating EDS. The following paragraphs describe the main subjective measures used.

The “Epworth Sleepiness Scale” (ESS) is the most widely adopted clinical tool to assess subjective sleepiness [79]. The ESS is a questionnaire asking the likelihood to doze off or fall asleep in eight different situations most people encounter in their daily lives. Responses range on a Likert scale from 0 to 3, with a total score from 0 to 24. A score higher than 10 is usually used to define EDS: the higher the score, the higher the subject’s risk of falling asleep during the day. Even though the ESS has good reliability (0.73–0.86), it suffers from several drawbacks. ESS was found to poorly correlate with AHI and OSA-related variables, with correlation coefficients from 0.11 to 0.23 [80]. ESS presents a natural tendency to underestimate EDS when patients complain of insomnia or have difficulties falling asleep. ESS overestimates EDS during some sleep-inducing conditions, which does not necessarily indicate problematic EDS depending on activities of daily life for different genders and ages [81, 82]. Furthermore, it should be emphasized that the ESS usually applies to clinical settings and populations, with a dearth of data about its psychometric properties in non-clinical samples, in particular among drivers. Notable driver studies include those by Baiardi and collaborators in a cohort of 221 commercial drivers [83], and those by Garbarino et al. in a sample of 283 truck drivers of dangerous goods [58], in a cohort of 526 truck drivers [84] and in a sample of 949 truck drivers [85, 86].

Questionnaires such as the ESS may provide more accurate results when compared with additional details from a partner [43]. Focused questions by the clinician on critical features of EDS may be more reliable than the ESS, such as investigating whether EDS is present when the individual is alone and non-active, or when mentally, physically, and socially engaged, and when performing high-risk activities, such as driving.

A systematic review of the literature has indicated higher correlations of the ESS score with other measures of EDS (the Maintenance of Wakefulness Test (MWT), $r = -0.43$, and the Multiple Sleep Latency Test (MSLT), $r = -0.27$) than with less strictly related constructs (severity of OSA and general health measures, pooled r ranging from 0.11 to 0.23), though all correlation coefficients were lower than expected [87]. The internal consistency of the ESS (Cronbach's alphas ranged from 0.7 to 0.9) suggests that this tool is trustworthy for group-level comparisons, but it should be used with caution for individual-level comparisons [87].

Other questionnaires evaluate the overall feeling of sleepiness, such as the Basic Nordic Sleepiness Questionnaire (BNSQ), by asking how often per week subjects complain EDS [88]. This question correlates with different factors that contribute to EDS, including snoring [89], nasal congestion [90], and OSA severity categories [91]. EDS is usually defined when subjects experience daytime sleepiness at least 3 days per week. The prevalence of EDS in the general population ranges from 17 to 28.5% by using BNSQ [92–94]. In sleep research, the BNSQ has been used together with the ESS to identify individuals with EDS at the wheel [1].

Another subjective tool used routinely is the "Stanford Sleepiness Scale" (SSS), initially developed as a 24-item true/false format and administered to 340 undergraduate students. The principal component analysis identified two main dimensions, each one explaining 24.2 and 20.6% of the total variance, respectively [95]. The SSS uses a self-rated seven-point scale of the same range to quantify symptoms [96]. The modified SSS is comprised of only one item on seven-point scale measuring levels of sleepiness throughout the day. A score of more than 3 points at any time when the respondent should be feeling alert indicates serious EDS [97]. The comparison between ESS and SSS in patients attending sleep clinics who receive information about sleepiness and fitness-to-drive [98] provide largely reproducible information when they report their symptoms.

The "Barcelona Sleepiness Index" (BSI) [99] was developed using focus groups in a sample of 53 consecutive patients and their bed partners. The patients were suffering from sleep-disordered breathing and complained of EDS. The tool was subsequently validated against objective measures in another sample of 98 consecutive patients suffering or not from EDS. The objective measures included the "Sustained Attention to Response Task" (SART), MWT, and MSLT. Two items achieved the highest predictive value for the MWT and were sensitive to treatment changes with continuous positive airway pressure, with an overall sensitivity and specificity of 64.9 and 72.1%, respectively.

The "Karolinska Sleepiness Scale" (KSS) gauges the subjective level of sleepiness at a given time of day, a measure of situational sleepiness. On this scale, subjects indicate which level best reflects the psychophysical state experienced in the last 10 min. This is a nine-point scale (1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy—but no difficulty remaining awake, and 9 = extremely sleepy—fighting sleep). A modified KSS exists and contains one other item, 10 = extremely sleepy, falls asleep all the time [100]. Since the KSS measures situational sleepiness rather than trait sleepiness, it has not been widely used for fitness to drive.

Objective measures

Both the MSLT and the MWT are the main objective test tools for EDS, and they are considered the gold standards for the detection of EDS in the clinical practice of sleep medicine [101]. It is important to note, however, that the reported broad variabilities of the MSLT and MWT sleep latencies in the healthy population overlap with findings in medical or sleep disorders characterized by EDS [102, 103].

The MSLT measures the underlying physiological tendency for a subject to fall asleep in lack of alerting factors [104]. The test takes place in the sleep laboratory after polysomnography of the previous night and consists of four or five nap opportunities performed at 2-h intervals. Being used worldwide, the MSLT is the most widely accepted objective measure of physiologic sleep tendency [102, 103].

The MWT, which is a laboratory-based daytime polysomnographic test, gauges the subject's ability to stay awake in a context with low levels of stimulation [102]. Mitler et al. [105] designed the test to measure daytime wakefulness when there are clinical issues that concern treatment efficacy or patient safety. Recording conditions during the MWT are similar to but not equal to those of the MSLT. The MWT is performed in a sequence of four tests at 2-h intervals beginning 1.5 to 3 h after the individual's standard waking time [103].

The task force of the AASM [101] underlined that the MSLT is not targeted to assess the effects of EDS in patients dealing with potentially dangerous circumstances (i.e., fitness to drive). On the contrary, the MWT, which requests patients to fight against sleepiness, is better adapted to evaluate fitness to drive [106]. During the 40-min MWT, abnormal sleep latency correlates with impaired driving as measured both on a driving simulator [107] and in real driving conditions [108] in untreated patients with OSA. Another study has confirmed that individuals with shorter sleep latencies on the MWT exhibit impaired driving performance compared to subjects with intermediate and long sleep latencies, regardless of their sleep diagnosis and whether being in treatment or not. This study supports the usefulness of the MWT as a reliable measure of EDS related to impairment for driving in patients with sleep disorders [106]. However, since both the MSLT and the MWT are rather expensive and somewhat impractical, and since they both require a sleep laboratory, there is a need to develop more straightforward, less expensive tests to evaluate objective EDS in patients with OSA to estimate their fitness to drive.

Several studies confirmed the negative effect of EDS on driving performance, as assessed by driving simulation (DS) or in real driving conditions [107, 109, 110]. Unfortunately, DS testing cannot be translated into fitness for real driving [84]. However, studies on DS in patients with OSA have assessed the relationship between objective EDS measurements and driving performance. These studies confirmed that tracking error on a divided-attention driving task correlated with MSLT sleep latencies in baseline conditions and improved after the use of CPAP therapy [111, 112]. The monotonous DS testing confirmed the correlation between MSLT sleep latencies and lane-position variability in patients with OSA [109]. DS performance correlated closer with MWT, compared with MSLT for the propensity to fall asleep, with ESS score > 11, and reported the previous history of road accident [109]. As a group, patients with OSA show lower steering performance and exhibit a higher number of road accidents than healthy age-matched controls. However, the variability in driving performance among patients is wide [113].

In a recent systematic review [114] comparing subjective and objective measures of driving performance and road safety, only two studies were examined considering sleep, drowsiness, and monotonous driving in DS. There was no significant time of the day compared to subjective measures of EDS, but there were significant increases in the occurrence of micro-sleeps at the end of the day [115]. Discrepancies between the self-report and objective measures of EDS (electroencephalography) suggest an impairment in the drivers' ability to evaluate their sleepiness [116].

As both subjective (ESS) and objective (MSLT) measures of EDS may lead to different results in clinical populations with OSA, previous studies have applied a twofold approach of identifying "sleepy" patients based on pairing subjective and objective sleepiness [117, 118]. Sforza et al. [119] compared different subjective (SSS) and objective (polysomnography or PSG, and MWT) measures of EDS in subjects with breathing disorders related to sleep using psychomotor vigilance testing (PVT). The PVT is a computer-based test with a chronometric measure of an individual's reaction time to specified small visual stimulation in a labile environment. The small changes are assessed at pseudo-random intervals ranging from 2 to 10 s [120, 121]. Individuals are trained to react quickly to a digital signal on a computer terminal by pressing a key. Errors of omission and commission are collected. Reaction times exceeding 500 ms or failure to react are defined lapses. The cumulative count of lapses is the principal outcome measure of PVT performance believed to represent perceptual, processing, or executive failures in the central nervous system. Count of lapses strictly correlates with the effects of sleep deprivation, sleep restriction, on attention, and vigilance [122–125]. Patients with OSA, compared to controls, show impairments in performance affecting both speed and accuracy. Lapses and false responses were outnumbered in patients with more severe EDS in the MWT, and with higher AHI, while analysis of omissions seems to be more sensitive to the assessment of diurnal impairment [119]. As a consequence of chronic sleep restriction or total sleep deprivation, EDS is associated with impaired PVT performance in a dose-response manner. In patients with OSA, objectively measured EDS via the MWT is associated with slower reaction time in PVT, whereas subjectively assessed EDS measured by ESS is associated with increased numbers of lapses [126].

Lapses in attention on the PVT reflect state instability linked with sleep deprivation. Lapses are the most common PVT metric used in the peer-reviewed literature [127]. Two lapses were reported to be the lowest threshold for discriminating between sleep-deprived and non-sleep-deprived individuals. Albeit the PVT measures the neurobehavioral alertness, it is sensitive to EDS induced through sleep deprivation and associated with OSA and is much less expensive and time-consuming compared with MSLT [54, 119, 126, 128].

Certification of fitness to drive in OSA-EDS patients: we have got something that might work but no guarantees

New EU legislation has been adopted on fitness-to-drive tasks for the detection, treatment, and management of drivers with an AHI of 15 or more in the presence of EDS. Overnight PSG is deemed the "gold standard" for the diagnosis of OSA. However, PSG is not widely available, and the expenses of time and money constitute a burden to public health resources.

The OSA Working Group under European Commission Directive 2006/126 proposed a questionnaire to screen for OSA (Q-OSAS) in order to identify driving license applicants at risk for OSA with EDS. The questionnaire is not mandatory, but member states are strongly encouraged to use it [129, 130]. Five factual elements are easily collected: gender, age, height, weight, and the history of recent MVAs involving injuries or property damage according to police reports. The OSA Working Group investigated the presence of snoring (frequency and intensity), of witnessed pauses in breathing as identified by bed partners, of EDS primarily while driving associated with the restorative quality of sleep, and the diagnosis of arterial hypertension. Most questions required YES/NO/DON'T KNOW answers. EDS can be explored using the ESS [129]. Unfortunately, the ESS shows only moderate correlation with objective measures of EDS in patients with OSA [131].

If patients know that admission of EDS may have implications regarding their driving license, they may give biased answers to questions using tools like the ESS. This behavior is mainly present in the case that patients' work depends upon a license to drive [98]. Patients attending sleep clinics do provide largely reproducible information on the ESS or the SSS; only 5.7% of them reconsiders and switches their score from sleepy to non-sleepy. Clinicians should inform patients about potential implications before compiling the ESS. Factors that play a role in the reliability of self-reported data include the setting of individuals' testing and whether or not results remain private [98].

Another limitation of the ESS was recently reported: feeling sleepy better correlates with many variables that contribute to EDS, such as restless leg syndrome and insomnia, rather than with the risk of dozing [94]. Quite often, sleepy subjects complain of not feeling restful during the day rather than referring sleepiness; they also complain of having a decidedly modest quality of life. Subjects at risk of dozing off during the day but not complaining EDS have comparable symptoms as the non-sleepy population, except for snoring and self-reported apnea [94]. Therefore, since it measures just one aspect of sleepiness, the ESS alone is not adequate to assess subjects for fitness to drive. [81, 132, 133].

Limitations

Several factors may condition the generalizability of the findings of this review. Comparing reported results is challenging due to the varying definitions of EDS, and the many different tools used to measure EDS, both subjectively and objectively. EDS and OSA severity are loosely correlated. Most subjects with moderate to severe OSA are not pathologically sleepy (50–80%), and approximately half of such subjects deny EDS [61, 134]. Fifty percent of the drivers who are habitually sleepy state that sleepiness occurs predominantly at the wheel while denying EDS during any other activities [21]. Residual EDS may remain even with optimal treatment of OSA with CPAP, suggesting that EDS may be related to other coexisting factors and comorbidities [135].

Considering sleepiness as a complex phenomenon with different subjective symptoms and objective correlates, each tool used to measure EDS explores different aspects with variable degrees of accuracy. While reasonably reliable in clinical settings, these tools are not accurate enough to characterize fitness to drive. There is no consensus on the method to use for assessing EDS in patients with OSA.

Future perspectives

The ideal tool for measuring sleepiness should be reliable, reproducible, widely available, inexpensive, and easy to perform. Since objective measures of EDS are unwieldy and expensive, and subjective measures of EDS are unreliable, the search for a predictive biomarker is now a target of the research in progress. Despite the publication of data on biomarkers in OSA, including the effect of treatment, research in this area is still at the beginning [136–139]. One promising biomarker is the proinflammatory cytokine IL-6, but there are conflicting data on its effects in OSA [140]. Bravo et al. [71] identified levels of IL-6 in a group of men with severe OSA compared with matched controls. Objective and subjective sleepiness was assessed using ESS and MSLT. OSA patients had higher levels of IL-6 compared with controls, but no differences emerged in IL-6 levels between OSA with and without sleepiness [71]. A significant relationship between objective sleepiness by MSLT and elevated IL-6 levels has been reported, but this relationship was not found for severe subjective sleepiness and IL-6 in OSA [72]. The researchers demonstrated a similar association of IL-6 levels with EDS identified by PVT and ESS and with subjective sleepiness, but they did not find an association of IL-6 with PVT measured sleepiness alone [62]. The potential usefulness of IL-6 as a biomarker of both physiological and residual sleepiness in treated OSA, regardless of other confounding factors such as obesity and sleep duration, needs further exploration 140–146]. A double approach to identify "sleepy" patients, based on combined subjective and objective sleepiness tests and physiological and biochemical biomarkers, may be more reliable than any single measure of EDS [147].

Conclusions

Sleepiness while driving has a significant impact on road safety, contributing to the burden of traffic-related morbidity and mortality. OSA is the most frequent medical cause of EDS. Further investigation is needed to clarify which patients with OSA are vulnerable to EDS while driving and to enhance predictive accuracy for driving risk in OSA.

Road safety programs should be strengthened to inform drivers with OSA about the risk involved with EDS at the wheel and improve their awareness of risk for EDS-related MVAs. Due to the relevant social and economic impact of EDS in professional and non-professional drivers, we recommend the implementation of screening programs for EDS.

Inexpensive, less time-consuming new tools are urgently needed for the objective evaluation of EDS in OSA patients for certification of driving license. Useful screening tools will most likely result from a combination of physiological and biochemical biomarkers.

Compliance with ethical standards

Conflict of interest Author Sergio Garbarino states that he has no conflict of interest.

Ethical approval This article does not contain any study with human participants or animals performed by any of the authors.

References

1. Quera-Salva MA, Hartley S, Sauvagnac-Quera R, Sagaspe P, Taillard J, Contrand B, Micoulaud JA, Lagarde E, Barbot F, Philip P (2016) Association between reported sleep need and sleepiness at the wheel: comparative study on French highways between 1996 and 2011. BMJ Open 6:e012382. https://doi.org/10.1136/bmjopen-2016-012382
2. Zwahlen D, Jackowski C, Pfäffli M (2016) Sleepiness, driving, and motor vehicle accidents: a questionnaire-based survey. J Forensic Legal Med 44:183–187. https://doi.org/10.1016/j.jflm.2016.10.014
3. Nabi H, Guéguen A, Chiron M et al (2006) Awareness of driving while sleepy and road traffic accidents: prospective study in GAZEL cohort. BMJ 333:75
4. Connor J, Norton R, Ameratunga S et al (2002) Driver sleepiness and risk of serious injury to car occupants: population based case–control study. BMJ 324:1125
5. Stutts JC, Wilkins JW, Scott Osberg J et al (2003) Driver risk factors for sleep-related crashes. Accid Anal Prev 35:321–331
6. Global status report on road safety 2018: summary. Geneva: World Health Organization; 2018 (WHO/NMH/NVI/18.20). Licence: CC BY-NC-SA 3.0 IGO). https://www.who.int/violence_injury_prevention/road_safety_status/2018/GSRRS2018_Summary_EN.pdf. Accessed December 2018
7. https://www.who.int/news-room/fact-sheets/detail/road-traffic-injuries. Accessed December 2018
8. Gonçalves M, Amici R, Lucas R, Åkerstedt T, Cirignotta F, Horne J, Léger D, McNicholas WT, Partinen M, Téran-Santos J, Peigneux P, Grote L, National Representatives as Study Collaborators (2015) Sleepiness at the wheel across Europe: a survey of 19 countries. J Sleep Res 24(3):242–253
9. Tefft BC (2012) Prevalence of motor vehicle crashes involving drowsy drivers, United States, 1999–2008. Accid Anal Prev 45:180–186
10. Philip P, Taillard J, Guilleminault C et al (1999) Long distance driving and self-induced sleep deprivation among automobile drivers. Sleep 22:475–480
11. de Mello MT, Narciso FV, Tufik S, Paiva T, Spence DW, Bahammam AS, Verster JC, Pandi-Perumal SR (2013) Sleep disorders as a cause of motor vehicle collisions. Int J Prev Med 4(3):246–257
12. Garbarino S, Nobili L, Beelke M, De Carli F, Ferrillo F (2001) The contributing role of sleepiness in highway vehicle accidents. Sleep 24(2):203–206
13. Bioulac S, Micoulaud-Franchi JA, Arnaud M, Sagaspe P, Moore N, Salvo F, Philip P (2017) Risk of motor vehicle accidents related to sleepiness at the wheel: a systematic review and meta-analysis. Sleep. 1(10):40. https://doi.org/10.1093/sleep/zsx134
14. Krieger J (2007) Sleep apnea and driving: how can this be dealt with? Eur Respir Rev 16(106):189–195
15. Mathis J, Seeger R, Ewert U (2003) Excessive daytime sleepiness, crashes and driving capability. Schweiz Arch Neurol Psychiatr 154(07):329–338
16. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, Mooser V, Preisig M, Malhotra A, Waeber G, Vollenweider P, Tafti M, Haba-Rubio J (2015) Prevalence of sleep disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 3(4):310–318
17. Findley LJ, Unverzagt ME, Suratt PM (1988) Automobile accidents involving patients with obstructive sleep apnea. Am Rev Respir Dis 138(2):337–340
18. Mulgrew AT, Nasvadi G, Butt A, Cheema R, Fox N, Fleetham JA, Ryan CF, Cooper P, Ayas NT (2008) Risk and severity of motor vehicle crashes in patients with obstructive sleep apnea/hypopnoea. Thorax. 63(6):536–541. https://doi.org/10.1136/thx.2007.085464
19. Garbarino S, Pitidis A, Giustini M, Taggi F, Sanna A (2015) Motor vehicle accidents and obstructive sleep apnea syndrome: a methodology to calculate the related burden of injuries. Chron Respir Dis 12(4):320–328. https://doi.org/10.1177/1479972315594624
20. Strohl KP, Brown DB, Collop N, George C, Grunstein R, Han F, Kline L, Malhotra A, Pack A, Phillips B, Rodenstein D, Schwab R, Weaver T, Wilson K, ATS Ad Hoc Committee on Sleep Apnea, Sleepiness, and Driving Risk in Noncommercial Drivers (2013) An official American Thoracic Society Clinical Practice Guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. Am J Respir Crit Care Med 187(11):1259–1266. https://doi.org/10.1164/rccm.201304-0726ST
21. Masa JF, Rubio M, Findley LJ (2000) Habitually sleepy drivers have a high frequency of automobile crashes associated with respiratory disorders during sleep. Am J Respir Crit Care Med 162(4 Pt 1):1407–1412
22. https://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:32014L0085. visited February 2019
23. Bonsignore MR, Randerath W, Riha R, Smyth D, Gratziou C, Goncalves M, McNicholas WT (2016) New rules on driver licensing for patients with obstructive sleep apnea: EU Directive 2014/85/EU. Eur Respir J 47(1):39–34
24. Grote L, Svedmyr S, Hedner J (2018) Certification of fitness to drive in sleep apnea patients: are we doing the right thing? J Sleep Res 27(6):e12719
25. Siegel JM (2009) Sleep viewed as a state of adaptive inactivity. Nat Rev Neurosci 10:747–753
26. Buxton OM, Cain SW, O'Connor SP, Porter JH, Duffy JF, Wang W, Czeisler CA, Shea SA (2012) Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Sci Transl Med 4(129):129ra43. https://doi.org/10.1126/scitranslmed.3003200
27. Garbarino S, Lanteri P, Durando P, Magnavita N, Sannita WG (2016) Co-morbidity, mortality, quality of life and the healthcare/welfare/social costs of disordered sleep: a rapid review. Int J Environ Res Public Health 13(8):E831
28. Goel N, Basner M, Rao H, Dinges DF (2013) Circadian rhythms, sleep deprivation, and human performance. Prog Mol Biol Transl

Sci 119:155–190. https://doi.org/10.1016/B978-0-12-396971-2.00007-5

29. Wittmann M, Dinich J, Merrow M, Roenneberg T (2006) Social jetlag: misalignment of biological and social time. Chronobiol Int 23(1–2):497–509
30. Gottlieb DJ, Redline S, Nieto FJ, Baldwin CM, Newman AB, Resnick HE, Punjabi NM (2006) Association of usual sleep duration with hypertension: the Sleep Heart Health Study. Sleep 29(8):1009–1014
31. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, Pickering TG, Rundle AG, Zammit GK, Malaspina D (2007) Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. Sleep 30(12):1667–1673
32. Borbély AA, Daan S, Wirz-Justice A, Deboer T (2016) The two-process model of sleep regulation: a reappraisal. J Sleep Res 25(2):131–143. https://doi.org/10.1111/jsr.12371
33. Johns MW (2010) A new perspective on sleepiness. Sleep Biol Rhythms 8:170–179. https://doi.org/10.1111/j.1479-8425.2010.00450.x
34. Saper CB, Cano G, Scammell TE (2005) Homeostatic, circadian, and emotional regulation of sleep. J Comp Neurol 493:92–98. https://doi.org/10.1002/cne.20770
35. Lockley, S. W., & Foster, R. G. (2012). Sleep: a very short introduction (Vol. 295). Oxford University Press
36. George PT (2018) The psycho-sensory wake drive—a power source for power naps and other common sleepwake phenomena: a hypothesis. Sleep Breath 22(1):41–48. https://doi.org/10.1007/s11325-017-1505-6
37. Moldofsky H (1992) Evaluation of daytime sleepiness. Clin Chest Med 13:417–425
38. Bliwise D (2001) Is the measurement of sleepiness the Holy Grail of sleep medicine? Am J Respir Crit Care Med 163:1517–1519
39. Cluydts R, De Valck E, Verstraeten E, Theys P (2002) Daytime sleepiness and its evaluation. Sleep Med Rev 6:83–96
40. Stepanski E (2002) Controversies in the measurement of daytime sleepiness. Sleep Med Rev 6:79–81
41. Ogilvie RD (2001) The process of falling asleep. Sleep Med Rev 5(3):247–270
42. American Academy of Sleep Medicine (2014) International Classification of Sleep Disorders, 3rd edn. American Academy of Sleep Medicine, Darien
43. Randerath W, Bassetti CL, Bonsignore MR, Farre R, Ferini-Strambi L, Grote L, Hedner J, Kohler M, Martinez-Garcia MA, Mihaicuta S, Montserrat J, Pepin JL, Pevernagie D, Pizza F, Polo O, Riha R, Ryan S, Verbraecken J, McNicholas WT (2018) Challenges and perspectives in obstructive sleep apnea: report by an ad hoc working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. Eur Respir J 52(3):1702616
44. Ohayon MM (2008) From wakefulness to excessive sleepiness: what we know and still need to know. Sleep Med Rev 12:129–141. https://doi.org/10.1016/j.smrv.2008.01.001
45. Sleep in America 2009 poll highlights & key findings. National Sleep Foundation. 2009. Available at: https://www.sleepfoundation.org/sites/default/files/inlinefiles/2009%20NSF%20POLL%20 PRESS%20RELEASE.pdf. Accessed May 2019
46. Roth T (2015) Effects of excessive daytime sleepiness and fatigue on overall health and cognitive function. J Clin Psychiatry 76(9):e1145
47. Gujar N, Yoo SS, Hu P, Walker MP (2011) Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. J Neurosci 31:4466–4474. https://doi.org/10.1523/JNEUROSCI.3220-10.2011
48. Womack SD, Hook JN, Reyna SH, Ramos M (2013) Sleep loss and risk-taking behavior: a review of the literature. Behav Sleep Med 11:343–359. https://doi.org/10.1080/15402002.2012.703628
49. Hisler G, Krizan Z (2019) Sleepiness and behavioral risk-taking: do sleepy people take more or less risk? Behav Sleep Med 17(3):364–377. https://doi.org/10.1080/15402002.2017.1357122
50. Carberry JC, Amatoury J, Eckert DJ (2018) Personalized management approach for OSA. Chest 153(3):744–755. https://doi.org/10.1016/j.chest.2017.06.011
51. Owens RL, Edwards BA, Eckert DJ, Jordan AS, Sands SA, Malhotra A, White DP, Loring SH, Butler JP, Wellman A (2015) An integrative model of physiological traits can be used to predict obstructive sleep apnea and response to non positive airway pressure therapy. Sleep 38(6):961–970. https://doi.org/10.5665/sleep.4750
52. Saaresranta T, Hedner J, Bonsignore MR, Riha RL, McNicholas WT, Penzel T, Anttalainen U, Kvamme JA, Pretl M, Sliwinski P, Verbraecken J, Grote L, ESADA study group (2016) Clinical phenotypes and comorbidity in European sleep apnea patients. PLoS One 11(10):e0163439. https://doi.org/10.1371/journal.pone.0163439
53. Garbarino S, Scoditti E, Lanteri P, Conte L, Magnavita N, Toraldo DM (2018) Obstructive sleep apnea with or without excessive daytime sleepiness: clinical and experimental data-driven phenotyping. Front Neurol 9:505
54. Silva GE, Goodwin JL, Vana KD, Quan SF (2016) Obstructive sleep apnea and quality of life: comparison of the SAQLI, FOSQ, and SF-36 questionnaires. Southwest J Pulm Crit Care 13(3):137–149
55. Lindberg E, Carter N, Gislason T, Janson C (2001) Role of snoring and daytime sleepiness in occupational accidents. Am J Respir Crit Care Med 164(11):2031–2035
56. Kapur VK, Resnick HE, Gottlieb DJ (2008) Sleep Heart Health Study Group. Sleep disordered breathing and hypertension: does self-reported sleepiness modify the association? Sleep 31(8):1127–1132
57. Ronksley PE, Hemmelgarn BR, Heitman SJ, Hanly PJ, Faris PD, Quan H, Tsai WH (2009) Obstructive sleep apnea is associated with diabetes in sleepy subjects. Thorax 64(10):834–839
58. Garbarino S, Guglielmi O, Campus C, Mascialino B, Pizzorni D, Nobili L, Mancardi GL, Ferini-Strambi L (2016) Screening, diagnosis, and management of obstructive sleep apnea in dangerous-goods truck drivers: to be aware or not? Sleep Med 25:98–104
59. Frost, Sullivan (2016) Hidden health crisis costing America billions. Under diagnosis and undertreating obstructive sleep apnea draining healthcare system. American Academy of Sleep Medicine, Darien (https://aasm.org/resources/pdf/sleep-apnea-economic-crisis.pdf visited May 2019)
60. Vgontzas AN (2008) Excessive daytime sleepiness in sleep apnea: it is not just apnea hypopnea index. Sleep Med 9(7):712–714
61. Roure N, Gomez S, Mediano O, Duran J, Pena Mde L, Capote F, Teran J, Masa JF, Alonso ML, Corral J et al (2008) Daytime sleepiness and polysomnography in obstructive sleep apnea patients. Sleep Med 9:727–731
62. Prasad B, Steffen AD, Van Dongen HPA, Pack FM, Strakovsky I, Staley B, Dinges DF, Maislin G, Pack AI, Weaver TE (2018) Determinants of sleepiness in obstructive sleep apnea. Sleep. https://doi.org/10.1093/sleep/zsx199
63. Punjabi NM, O'hearn DJ, Neubauer DN, Nieto FJ, Schwartz AR, Smith PL, Bandeen-Roche K (1999) Modeling hypersomnolence in sleepdisordered breathing. A novel approach using survival analysis. Am J Respir Crit Care Med 159(6):1703–1709
64. Batool-Anwar S, Kales SN, Patel SR, Varvarigou V, DeYoung PN, Malhotra A (2014) Obstructive sleep apnea and psychomotor vigilance task performance. Nat Sci Sleep 6:65–71

65. Lee IS, Bardwell WA, Ancoli-Israel S, Dimsdale JE (2010) Number of lapses during the psychomotor vigilance task as an objective measure of fatigue. J Clin Sleep Med 6(2):163–168
66. Sharkey KM, Orff HJ, Tosi C, Harrington D, Roye GD, Millman RP (2013) Subjective sleepiness and daytime functioning in bariatric patients with obstructive sleep apnea. Sleep Breath 17(1):267–274
67. Malhotra A, White DP (2002) Obstructive sleep apnea. Lancet 360(9328):237–245
68. Jordan AS, McSharry DG, Malhotra A (2014) Adult obstructive sleep apnea. Lancet 383(9918):736–747
69. Slater G, Pengo MF, Kosky C, Steier J (2013) Obesity as an independent predictor of subjective excessive daytime sleepiness. Respir Med 107(2):305–309
70. Gozal D, Serpero LD, Kheirandish-Gozal L, Capdevila OS, Khalyfa A, Tauman R (2010) Sleep measures and morning plasma TNFalpha levels in children with sleep-disordered breathing. Sleep 33(3):319–325
71. Bravo Mde L, Serpero LD, Barceló A, Barbé F, Agustí A, Gozal D (2007) Inflammatory proteins in patients with obstructive sleep apnea with and without daytime sleepiness. Sleep Breath 11(3):177–185
72. Li Y, Vgontzas AN, Fernandez-Mendoza J, Kritikou I, Basta M, Pejovic S, Gaines J, Bixler EO. (2017) Objective, but not subjective, sleepiness is associated with inflammation in sleep apnea. Sleep. ;40(2). doi: https://doi.org/10.1093/sleep/zsw033
73. DeMartino T, Ghoul RE, Wang L, Bena J, Hazen SL, Tracy R, Patel SR, Auckley D, Mehra R (2016) Oxidative stress and inflammation differentially elevated in objective versus habitual subjective reduced sleep duration in obstructive sleep apnea. Sleep 39(7):1361–1369. https://doi.org/10.5665/sleep.5964
74. Priou P, Le Vaillant M, Meslier N, Paris A, Pigeanne T, Nguyen XL, Alizon C, Bizieux-Thaminy A, Leclair-Visonneau L, Humeau MP, Gagnadoux F, IRSR sleep cohort group (2014) Cumulative association of obstructive sleep apnea severity and short sleep duration with the risk for hypertension. PLoS One 9: e115666
75. Garbarino S, Guglielmi O, Sanna A, Mancardi GL, Magnavita N (2016) Risk of occupational accidents in workers with obstructive sleep apnea: systematic review and meta-analysis. Sleep 39(6): 1211–1218. https://doi.org/10.5665/sleep.5834
76. Sanna A, Passali D, De Benedetto M, Marano G, Loglisci M, Garbarino S (2017) Obstructive sleep apnea syndrome and public health: the Italian way. Sleep Breath 21(4):995–996
77. Ferini-Strambi L, Sforza M, Poletti M, Giarrusso F, Galbiati A (2017) Daytime sleepiness: more than just obstructive sleep apnea (OSA). Med Lav 108(4):260–266. https://doi.org/10.23749/mdl.v108i4.6497
78. Murray BJ (2017) Subjective and objective assessment of hypersomnolence. Sleep Med Clin 12(3):313–322
79. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 14:540–545
80. Kingshott RN, Sime PJ, Engleman HM, Douglas NJ (1995) Self assessment of daytime sleepiness: patient versus partner. Thorax 50:994–995
81. Baldwin CM, Kapur VK, Holberg CJ, Rosen C, Nieto FJ, Sleep Heart Health Study Group (2004) Associations between gender and measures of daytime somnolence in the Sleep Heart Health Study. Sleep 27:305–311
82. Ulander M, Arestedt K, Svanborg E, Johansson P, Broström A (2013) The fairness of the Epworth Sleepiness Scale: two approaches to differential item functioning. Sleep Breath 17:157–165. https://doi.org/10.1007/s11325-012-0664-8
83. Baiardi S, La Morgia C, Sciamanna L, Gerosa A, Cirignotta F, Mondini S (2018) Is the Epworth Sleepiness Scale a useful tool for screening excessive daytime sleepiness in commercial drivers? Accid Anal Prev 110:187–189
84. Guglielmi O, Magnavita N, Garbarino S (2018) Sleep quality, obstructive sleep apnea, and psychological distress in truck drivers: a cross-sectional study. Soc Psychiatry Psychiatr Epidemiol 53(5):531–536
85. Garbarino S, Durando P, Guglielmi O, Dini G, Bersi F, Fornarino S, Toletone A, Chiorri C, Magnavita N (2016) Sleep apnea, sleep debt and daytime sleepiness are independently associated with road accidents. A cross-sectional study on truck drivers. PLoS One 11(11):e0166262
86. Garbarino S, Magnavita N, Guglielmi O, Maestri M, Dini G, Bersi FM, Toletone A, Chiorri C, Durando P (2017) Insomnia is associated with road accidents. Further evidence from a study on truck drivers. PLoS One 12(10):e0187256
87. Kendzerska TB, Smith PM, Brignardello-Petersen R, Leung RS, Tomlinson GA (2014) Evaluation of the measurement properties of the Epworth Sleepiness Scale: a systematic review. Sleep Med Rev 18(4):321–331
88. Partinen M, Gislason T (1995) Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. J Sleep Res 4:150–155
89. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993) The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328:1230–1235
90. Young T, Finn L, Kim H (1997) Nasal obstruction as a risk factor for sleep-disordered breathing. The University of Wisconsin Sleep and Respiratory Research Group. J Allergy Clin Immunol 99: S757–S762. https://doi.org/10.1016/s0091-6749(97)70124-6
91. Young T, Hutton R, Finn L, Badr S, Palta M (1996) The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? Arch Intern Med 156:2445–2451. https://doi.org/10.1001/archinte.1996.00440200055007
92. Hara C, Lopes Rocha F, Lima, Costa MF (2004) Prevalence of excessive daytime sleepiness and associated factors in a Brazilian community: the Bambui study. Sleep Med 5:31–36. https://doi.org/10.1016/j.sleep.2003.09.009
93. Kallin SA, Lindberg E, Sommar JN, Bossios A, Ekerljung L, Malinovschi A, Middelveld R, Janson C (2018) Excessive daytime sleepiness in asthma: what are the risk factors? J Asthma 55(8):844–850. https://doi.org/10.1080/02770903.2016.1263316
94. Thorarinsdottir EH, Bjornsdottir E, Benediktsdottir B, Janson C, Gislason T, Aspelund T, Kuna ST, Pack AI, Arnardottir ES (2019) Definition of excessive daytime sleepiness in the general population: feeling sleepy relates better to sleep-related symptoms and quality of life than the Epworth Sleepiness Scale score. Results from an epidemiological study. J Sleep Res 10:e12852. https://doi.org/10.1111/jsr.12852
95. MacLean AW, Fekken GC, Saskin P, Knowles JB (1992) Psychometric evaluation of the Stanford Sleepiness Scale. J Sleep Res 1:35–39
96. Hoddes E, Dement WC, Zarcone V (1972) The development and use of the Stanford Sleepiness Scale (SSS). Psychophysiology 9: 150
97. Herscovitch J, Broughton R (1981) Sensitivity of the Stanford Sleepiness Scale to the effects of cumulative partial sleep deprivation and recovery oversleeping. Sleep 4(1):83–91
98. Ayeni A, Beghal GS, Pengo MF, Shah N, Steier J (2019) Self-reported sleepiness in the context of fitness-to-drive. Sleep Breath. https://doi.org/10.1007/s11325-019-01810-w
99. Guaita M, Salamero M, Vilaseca I, Iranzo A, Montserrat JM, Gaig C, Embid C, Romero M, Serradell M, Leon C, de Pablo J, Santamaria J (2015) The Barcelona Sleepiness Index: a new instrument to assess excessive daytime sleepiness in sleep disordered breathing. J Clin Sleep Med 11:1289–1298

100. Miley AÅ, Kecklund G, Åkerstedt T (2016) Comparing two versions of the Karolinska Sleepiness Scale (KSS). Sleep Biol Rhythms 14(3):257–260. https://doi.org/10.1007/s41105-016-0048-8
101. Littner MR, Kushida C, Wise M et al (2005) Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. An American Academy of Sleep Medicine report. Sleep 28:113–121
102. Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB (2005) The clinical use of the MSLT and MWT. Sleep 28:123–44. 104
103. Wise MS (2006) Objective measures of sleepiness and wakefulness: application to the real world? J Clin Neurophysiol 23(1):39–49
104. Carskadon MA, Dement WC (1982) Nocturnal determinants of daytime sleepiness. Sleep 5(Suppl 2):S73–S81
105. Mitler MM, Gujavarty KS, Browman CP (1982a) Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. Electroencephalogr Clin Neurophysiol 53:658–661
106. Philip P, Chaufton C, Taillard J, Sagaspe P, Léger D, Raimondi M, Vakulin A, Capelli A (2013) Maintenance of Wakefulness Test scores and driving performance in sleep disorder patients and controls. Int J Psychophysiol 89(2):195–202. https://doi.org/10.1016/j.ijpsycho.2013.05.013
107. Sagaspe P, Taillard J, Chaumet G, Guilleminault C, Coste O, Moore N et al (2007) Maintenance of wakefulness test as a predictor of driving performance in patients with untreated obstructive sleep apnea. Sleep 30(3):327–330
108. Philip P, Sagaspe P, Taillard J, Chaumet G, Bayon V, Coste O et al (2008) Maintenance of Wakefulness Test, obstructive sleep apnea syndrome, and driving risk. Ann Neurol 64(4):410–416
109. Pizza F, Contardi S, Mondini S, Trentin L, Cirignotta F (2009) Daytime sleepiness and driving performance in patients with obstructive sleep apnea: comparison of the MSLT, the MWT, and a simulated driving task. Sleep. 32(3):382–391
110. George CF (2003) Driving simulators in clinical practice. Sleep Med Rev 7:311–320
111. George CF, Boudreau AC, Smiley A (1996) Simulated driving performance in patients with obstructive sleep apnea. Am J Respir Crit Care Med 154:175–181
112. George CF, Boudreau AC, Smiley A (1997) Effects of nasal CPAP on simulated driving performance in patients with obstructive sleep apnea. Thorax 52:648–653
113. Vakulin A, Catcheside PG, Baulk SD, Antic NA, Banks S, Dorrian J, McEvoy RD (2014) Individual variability and predictors of driving simulator impairment in patients with obstructive sleep apnea. J Clin Sleep Med 10(6):647–655. https://doi.org/10.5664/jcsm.3792
114. Kaye SA, Lewis I, Freeman J (2018) Comparison of self-report and objective measures of driving behavior and road safety: a systematic review. J Saf Res 65:141–151. https://doi.org/10.1016/j.jsr.2018.02.012
115. Moller HJ, Kayumov L, Bulmash EL, Nhan J, Shapiro CM (2006) Simulator performance, microsleep episodes, and subjective sleepiness: normative data using convergent methodologies to assess driver drowsiness. J Psychosom Res 61(3):335–342. https://doi.org/10.1016/j.jpsychores.2006.04.007
116. Schmidt EA, Schrauf M, Simon M, Fritzsche M, Buchner A, Kincses WE (2009) Drivers' misjudgement of vigilance state during prolonged monotonous daytime driving. Accid Anal Prev 41(5):1087–1093
117. Olson LG, Cole MF, Ambrogetti A (1998) Correlations among Epworth Sleepiness Scale scores, multiple sleep latency tests and psychological symptoms. J Sleep Res 7(4):248–253
118. Kritikou I, Basta M, Vgontzas AN, Pejovic S, Liao D, Tsaoussoglou M, Bixler EO, Stefanakis Z, Chrousos GP (2014) Sleep apnea, sleepiness, inflammation and insulin resistance in middle-aged males and females. Eur Respir J 43(1):145–155
119. Sforza E, Haba-Rubio J, De Bilbao F, Rochat T, Ibanez V (2004) Performance vigilance task and sleepiness in patients with sleep-disordered breathing. Eur Respir J 24(2):279–285
120. Dinges DF, Powell JW (1985) Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Methods Instrum Comput 17:652. https://doi.org/10.3758/BF03200977
121. Gillberg M, Kecklund G, Akerstedt T (1994) Relations between performances and subjective ratings of sleepiness during a night awake. Sleep 17:236–241
122. Dorrian J, Hursh S, Waggoner L, Grant C, Pajcin M, Gupta C, Coates A, Kennaway D, Wittert G, Heilbronn L, Vedova CD, Banks S (2019) How much is left in your "sleep tank"? Proof of concept for a simple model for sleep history feedback. Accid Anal Prev 126:177–183. https://doi.org/10.1016/j.aap.2018.01.007
123. Nir Y, Andrillon T, Marmelshtein A, Suthana N, Cirelli C, Tononi G, Fried I (2017) Selective neuronal lapses precede human cognitive lapses following sleep deprivation. Nat Med 23(12):1474–1480. https://doi.org/10.1038/nm.4433
124. Li Y, Vgontzas A, Kritikou I, Fernandez-Mendoza J, Basta M, Pejovic S, Gaines J, Bixler EO (2017) Psychomotor vigilance test and its association with daytime sleepiness and inflammation in sleep apnea: clinical implications. J Clin Sleep Med 13(9):1049–1056. https://doi.org/10.5664/jcsm.6720
125. Kitamura T, Miyazaki S, Kadotani H, Kanemura T, Sulaiman HB, Takeuchi S, Tabata T, Suzuki H (2018) Non-REM sleep-disordered breathing affects performance on the psychomotor vigilance task. Sleep Breath 22(2):329–335
126. Pejovic S, Basta M, Vgontzas AN, Kritikou I, Shaffer ML, Tsaoussoglou M, Stiffler D, Stefanakis Z, Bixler EO, Chrousos GP (2013) Effects of recovery sleep after one work week of mild sleep restriction on interleukin-6 and cortisol secretion and daytime sleepiness and performance. Am J Physiol Endocrinol Metab 305(7):E890–E896
127. Basner M, Dinges DF (2011) Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. Sleep 34(5):581–591
128. Kim H, Dinges DF, Young T (2007) Sleep-disordered breathing and psychomotor vigilance in a communitybased sample. Sleep 30(10):1309–1316
129. McNicholas W, editor. New standards and guidelines for drivers with obstructive sleep apnea syndrome. Report of the Obstructive Sleep Apnea Working Group [Internet]. Brussels: European Commission; 2013 [. Available from: https://ec.europa.eu/transport/road_safety/sites/roadsafety/files/pdf/behavior/sleep_apnea.pdf (visited May 2019)
130. Feketeová E, Mucska I, Klobučníková K, Grešová S, Stimmelová J, Paraničová I, Trojová I, Rosenberger J, Rimárová K, Dorko E (2018) EU questionnaire to screen for obstructive sleep apnea validated in Slovakia. Cent Eur J Public Health 26(Suppl):S32–S36. https://doi.org/10.21101/cejph.a5278
131. Nunes FS, Danzi-Soares NJ, Genta PR, Drager LF, Cesar LA, Lorenzi-Filho G (2015) Critical evaluation of screening questionnaires for obstructive sleep apnea in patients undergoing coronary artery bypass grafting and abdominal surgery. Sleep Breath 19(1):115–122
132. Adams RJ, Appleton SL, Vakulin A, Lang C, Martin SA, Taylor AW, Wittert GA (2016) Association of daytime sleepiness with obstructive sleep apnea and comorbidities varies by sleepiness definition in a population cohort of men. Respirology 21:1314–1321. https://doi.org/10.1111/resp.12829
133. Pilcher JJ, Pury CL, Muth ER (2003) Assessing subjective daytime sleepiness: an internal state versus behavior approach. Behav Med 29:60–67
134. Huamani C, Rey de Castro J, Mezones-Holguin E (2014) Sleepiness and nocturnal hypoxemia in Peruvian men with obstructive sleep apnea. Sleep Breath 18:467–473

135. Antic NA, Catcheside P, Buchan C, Hensley M, Naughton MT, Rowland S, Williamson B, Windler S, McEvoy RD (2011) The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. Sleep 34(1):111–119
136. Pack AI (2016) Application of personalized, predictive, preventative, and participatory (P4) medicine to obstructive sleep apnea. A roadmap for improving care? Ann Am Thorac Soc 13:1456–1467
137. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, Pepin JL (2015) Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. Sleep Med Rev 21:23–38
138. Sanchez-de-la-Torre M, Khalyfa A, Sanchez-de-la-Torre A, Martinez-Alonso M, Martinez-Garcia MA, Barcelo A, Lloberes P, Campos-Rodriguez F, Capote F, Diaz-de-Atauri MJ, Somoza M, Gonzalez M, Masa JF, Gozal D, Barbe F (2015) Precision medicine in patients with resistant hypertension and obstructive sleep apnea: blood pressure response to continuous positive airway pressure treatment. J Am Coll Cardiol 66:1023–1032
139. Schwarz EI, Martinez-Lozano Sinues P, Bregy L, Gaisl T, Garcia Gomez D, Gaugg MT, Suter Y, Stebler N, Nussbaumer-Ochsner Y, Bloch KE, Stradling JR, Zenobi R, Kohler M (2016) Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnea. Thorax 71:110–117
140. Vgontzas AN, Bixler EO, Lin HM, Prolo P, Trakada G, Chrousos GP (2005) IL-6 and its circadian secretion in humans. Neuroimmunomodulation 12(3):131–140
141. Luz GP, Guimarães TM, Weaver TE, Nery LE, Silva LO, Badke L, Coelho G, Millani-Carneiro A, Tufik S, Bittencourt L (2016) Impaired sustained attention and lapses are present in patients with mild obstructive sleep apnea. Sleep Breath 20(2):681–687
142. Larue GS, Rakotonirainy A, Pettitt AN (2011) Driving performance impairments due to hypovigilance on monotonous roads. Accid Anal Prev 43:2037–2046
143. Kim H, Young T (2005) Subjective daytime sleepiness: dimensions and correlates in the general population. Sleep 28:625–634
144. Arnardottir ES, Maislin G, Schwab RJ, Staley B, Benediktsdottir B, Olafsson I, Juliusson S, Romer M, Gislason T, Pack AI (2012) The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. Sleep 35(7):921–932. https://doi.org/10.5665/sleep.1952
145. Sunwoo BY, Jackson N, Maislin G, Gurubhagavatula I, George CF, Pack AI (2012) Reliability of a single objective measure in assessing sleepiness. Sleep 35(1):149–158. https://doi.org/10.5665/sleep.1606
146. Zhang C, Varvarigou V, Parks PD, Gautam S, Bueno AV, Malhotra A, Kales SN (2012) Psychomotor vigilance testing of professional drivers in the occupational health clinic: a potential objective screen for daytime sleepiness. J Occup Environ Med 54(3):296–302
147. Fleming WE, Ferouz-Colborn A, Samoszuk MK, Azad A, Lu J, Riley JS, Cruz AB, Podolak S, Clark DJ, Bray KR, Southwick PC (2016) Blood biomarkers of endocrine, immune, inflammatory, and metabolic systems in obstructive sleep apnea. Clin Biochem 49(12):854–861