Evidence Report

Obstructive Sleep Apnea and Commercial Motor Vehicle Driver Safety (Comprehensive Review)

Volume I

Presented to

Federal Motor Carrier Safety Administration

November 21, 2007

Prepared for

MANILA Consulting Group, Inc.
1420 Beverly Road, Suite 220
McLean, VA 22101

Prepared by

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

Evidence reports are sent to the Federal Motor Carrier Safety Administration's (FMCSA) Medical Review Board (MRB) and Medical Expert Panels (MEPs). The MRB and MEPs make recommendations on medical topics of concern to FMCSA.

FMCSA will consider all MRB and MEPs recommendations; however, all proposed changes to current standards and guidelines will be subject to public notice and comment and relevant rulemaking processes.

Policy Statement

This report was prepared by ECRI Institute under subcontract to MANILA Consulting Group, Inc., which holds prime GS-10F-0177N/DTMC75-06-F-00039 with the Department of Transportation's Federal Motor Carrier Safety Administration. ECRI Institute is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI Institute has been designated an Evidence-based Practice Center by the United States Agency for Healthcare Research and Quality. ECRI Institute's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI Institute's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this evidence report is to provide information regarding the current state of knowledge on this topic. It is not intended as instruction for medical practice, or for making decisions regarding individual patients.

Table of Contents

Tables

Figures

Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12% of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the United States Department of Transportation (DOT), there were 4,932 fatal crashes involving a large truck in 2005 for a total of 5,212 fatalities. In addition, there were 137,144 nonfatal crashes; 59,405 of these were crashes that resulted in an injury to at least one individual (for a total of 89,681 injuries).

The purpose of this evidence report is to address several key questions posed by Federal Motor Carrier Safety Administration (FMCSA). Each of these key questions was developed by FMCSA so that the answers to these questions would provide information that would be useful in updating its current medical examination guidelines. The seven key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with obstructive sleep apnea (OSA) at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Key Question 2: What disease-related factors are associated with an increased motor vehicle crash risk among individuals with OSA?

Key Question 3: Given the findings of Key Question 2, are individuals with OSA unaware of the presence of the factors that appear to be associated with an increased motor vehicle crash risk?

Key Question 4: Are there screening/diagnostic tests available that will enable examiners to identify those individuals with OSA who are at an increased risk for a motor vehicle crash?

Key Question 5: Which treatments have been shown to effectively reduce crash risk among individuals with OSA? Where reductions in crash risk have been assessed:

i. directly (crash risk)
ii. quasi-directly (simulated driving performance)
iii. indirectly (OSA severity, excessive daytime sleepiness, cognitive and psychomotor function, blood pressure, SaO_2)

Key Question 6: What is the length of time required following initiation of an effective treatment (determined by Key Question 5) for patients with OSA to reach a degree of improvement that would permit safe driving (as determined by crash rates or through indirect measures[1] of crash risk)?

Key Question 7: How soon, following cessation of treatment (e.g., as a consequence of noncompliance), will individuals with OSA demonstrate reduced driver safety (as determined by crash rates or through indirect measures of crash risk)?

[1] Indirect measures of driver safety include the following: simulated driving, closed course driving, measures of cognitive function, measures of psychomotor function, and daytime sleepiness.

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by this evidence report were identified using a process consisting of a comprehensive search of the literature; examination of abstracts of identified studies in order to determine which articles would be retrieved; and the selection of the actual articles that would be included in each evidence base.

A total of seven electronic databases (MEDINE, PubMed (PreMEDLINE), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library) were searched (through April 30, 2007). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant articles not identified by our electronic searches. Hand searches of the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria that were determined *a priori.*

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account not only the quality of the individual studies that comprise the evidence base for each key question; we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Analytic Methods

The set of analytic techniques used in this evidence report was extensive. Random- and fixed-effects meta-analyses were used to pool data from different studies.(1-5) Differences in the findings of studies (heterogeneity) were identified using the Q-statistic and I^2.(6-8) Sensitivity analyses, aimed at testing the robustness of our findings, included the use of cumulative fixed- and random-effects meta-analysis.(9-11) The presence of publication bias was tested for using the "trim and fill" method.(12-14)

Presentation of Findings

In presenting our findings we made a clear distinction between qualitative and quantitative conclusions, and we assigned a separate "strength of evidence" rating to each of conclusion format. The strength-of-evidence ratings assigned to these different types of conclusions are defined in Table 1.

Table 1. Strength-of-evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Minimally acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI Institute recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI Institute recommends frequent monitoring of the relevant literature.

Strength of Evidence	Interpretation
Quantitative Conclusion (Stability of Effect-Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

Evidence-based Conclusions

Key Question 1: Are individuals with OSA at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Seventeen articles describing 17 unique studies met the inclusion criteria for Key Question 1. Four of the 17 included studies were graded as being moderate quality. The remaining 11 studies were graded as low quality. Two included studies enrolled distinct populations of commercial motor vehicle (CMV) drivers. The remainder of the studies included private motor vehicle license holders, an unknown number of whom may have held commercial driver licenses.

A number of evidence-based conclusions were drawn from the findings of our analyses of the data extracted from the 17 included studies. These conclusions are presented below:

Drivers of CMVs

- **CMV drivers with OSA are at an increased risk for a crash when compared to their counterparts who do not have the disorder (Strength of Evidence: Minimally Acceptable).**
    - **A precise estimate of the magnitude of this increased risk cannot be determined at this time.**

    Two studies presented data directly relevant to the question of whether OSA has an impact on CMV driver safety. One study compared crash risk among drivers with SAS (symptom diagnosis) and drivers not diagnosed with SAS (controls). Drivers diagnosed with SAS (Multivariable Apnea Prediction Score ≥0.5 and Epworth Sleepiness Scale (ESS) score ≥11) were found to be at an increased risk for motor vehicle crash (odds ratio (OR) = 1.3, 95% 1.00-1.69). The value of this study's findings is weakened somewhat by the fact that individuals enrolled in the study were diagnosed with sleep apnea using questionnaires only.

    The second study found that truck drivers identified with sleep-disordered breathing (SDB) had a two-fold higher crash rate per mile than drivers without SDB. Crash frequency was not dependent on the severity of the sleep-related breathing disorder. Obese drivers with a body mass ≥30 kg/m^2 also presented a two-fold higher crash rate than nonobese drivers. In addition, the authors found that a complaint of excessive daytime sleepiness was related to a significantly higher automotive crash rate in long-haul commercial truck drivers. SDB with hypoxemia and obesity are risk factors for automotive crashes.

Drivers of Non-CMVs

Because data from studies of CMV drivers with OSA is scarce, we deemed it worthwhile to examine relevant data from studies that investigated crash risk associated with OSA among more general driver populations. While the generalizability of the findings of these studies to CMV drivers may not be clear, such findings do at the very least allow one the opportunity to draw evidence-based conclusions about the relationship between OSA and motor vehicle crash risk in general.

- **As a group, drivers with OSA are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Strong).**
    - **A precise estimate of the magnitude of this increased risk cannot be determined at the present time.**

  Nine studies (Quality Rating: Low) provided data on the relative incidence of crash among individuals who have OSA and comparable individuals without the disorder. Pooling of these data using a random-effects meta-analysis revealed that the mean crash-rate ratio associated with OSA is likely to fall within the range of 1.30 to 5.72 (95% CI of random-effects summary effect-size estimate). Thus, if the underlying crash risk for a CMV driver is 0.08 crashes per person-year, the crash risk for a CMV driver with OSA can be expected to be in the range of 0.10 to 0.46 crashes per person-year. A series of sensitivity analyses found that the estimate was robust. While the quality of the studies was not high, the data were qualitatively consistent, making it unlikely that future studies will overturn our finding that individuals with OSA are at increased risk for a motor vehicle crash.

Key Question 2: What disease-related factors are associated with an increased motor vehicle crash risk among individuals with OSA?

Our assessment of the evidence pertaining to Key Question 1 found that drivers with OSA (both commercial and noncommercial) are at a significantly increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder. Not all individuals with OSA, however, appear to be at increased risk and many individuals with the disorder do not pose an additional threat to public safety. The aim of Key Question 2 was to determine whether there are specific risk factors that are predictive of which individuals with OSA are at the greatest risk for a crash. The identification of such risk factors is important, because it will enable medical examiners to differentiate high-risk individuals from low-risk individuals when making decisions about fitness-to-drive certification.

Ten articles describing 10 unique studies met the inclusion criteria for Key Question 2. The quality of the included studies, all of which utilized a case-control design, was not high. One of the 10 included studies was graded as being of moderate quality. The remaining nine studies were graded as being of low quality. One of the studies assessed the factors predictive of crash among CMV drivers with OSA.

The findings of our analyses of the data extracted from the 10 included studies that addressed Key Question 2 are as follows:

- **No evidence-based conclusion pertaining to the risk factors for crash among CMV drivers with OSA can be drawn at the present time.**

  A single study examined the relationship between several potential risk factors for crash in CMV drivers. Potential risk factors assessed included the presence of excessive daytime sleepiness (measured using a nonvalidated instrument), and severity of SDB (as measured using the Oxygen Desaturation Index (ODI) and body mass index (BMI)). The study investigators found that

the presence of excessive daytime sleepiness was associated with an increased crash risk. However, neither the severity of SDB nor BMI were found to be significantly associated with crash risk. Because of the low power of this study to detect the presence of these latter associations, and the fact that an underlying trend suggests that these factors are associated with crash risk, it cannot be concluded that no association exists (a potential type-II statistical error) based on the findings of this study alone.

- **Four factors have been shown to be associated with crash risk among the general driver population. These factors are the presence and degree of daytime sleepiness (as measured using the ESS, but not Multiple Sleep Latency Test [MSLT] or Maintenance of Wakefulness Test[MWT]), severity of disordered respiration during sleep (as measured by the Apnea-Hypopnea Index [AHI] or the Respiratory Disturbance Index[RDI]), blood SaO_2 levels, and BMI (Strength of Evidence: Minimally Acceptable).**

  A total of nine included studies that enrolled drivers with private motor vehicles addressed Key Question 2. Potential risk factors examined by these studies included BMI, the presence and severity of daytime sleepiness, the severity of disordered respiration, SaO_2, various measures of cognitive and psychomotor function, and measures of depression. Taking the data from all nine studies into account, four factors were found to be associated with crash risk. These factors were the presence and degree of daytime sleepiness (as measured using the ESS but not the MSLT or MWT), severity of disordered respiration during sleep (as measured by the AHI or the RDI), blood SaO_2 levels, and the BMI. The remaining potential risk factors were not assessed by more than one included study. Consequently, we refrain from drawing evidence-based conclusions about the relationship between cognitive and psychomotor function and measures of depression at this time.

Key Question 3: Given the findings of Key Question 2, are individuals with OSA unaware of the presence of the factors that appear to be associated with an increased motor vehicle crash risk?

Our aim in addressing Key Question 3 was to determine whether individuals with OSA are aware of the presence and/or severity of factors that have been shown to be associated with an increased risk for a motor vehicle crash in this population. Our analyses for Key Question 2 identified four such risk factors: BMI; the severity of apnea and hypopnea (as measured using HDI or RDI); the presence and severity of oxygen desaturation; and the presence and severity of excessive daytime sleepiness (as measured by the ESS, MWLT, or MWT)

Key Question 3 is only relevant to one of these four risk factors; it is unrealistic to posit that an obese individual may be unaware of his/her condition. Also, it is highly likely that an individual with OSA will be unaware of the number of apneic and hypopneic events that he/she experiences during the night and his/her SaO_2 levels. Consequently, we confined this question to one risk factor: daytime sleepiness.

Three articles describing three unique studies met the inclusion criteria for Key Question 3. None of the three studies, all of which were case series, was of high quality and none attempted to determine whether CMV drivers are aware of the extent to which they are affected by daytime sleepiness.

The finding of our analysis of the data extracted from the three included studies that addressed Key Question 3 is as follows:

- **Individuals with OSA may not be aware of the extent to which they are affected by daytime sleepiness (Strength of Evidence: Minimally Acceptable).**

  Three included studies addressed Key Question 3. One included study found that individuals with moderate-to-severe OSA re-evaluated the degree of sleepiness they had experienced prior to the onset of treatment measured using the ESS: the pretreatment level of sleepiness was reassessed as being much higher than originally reported. Another included study found no correlation between ESS and MSLT scores suggesting a disconnect between subjective and objective measures of sleepiness. However, the final included study compared ESS scores from individuals with OSA with that estimated by their partner.

Key Question 4: Are there screening/diagnostic tests available that will enable examiners to identify those individuals with OSA who are at an increased risk for a motor vehicle crash?

The current reference standard study for diagnosing and determining the severity of OSA is in-laboratory, technician-attended polysomnography (PSG). Among other physiological parameters such as air flow, heart rate and rhythm, and respiratory effort, PSG assesses all four of the known risk factors for crash listed above. This has led to suggestions that all individuals who wish to be certified to drive a CMV and are suspected of, or diagnosed with, OSA, should undergo overnight PSG at a specialist sleep center. For example, the September 2006 recommendations regarding the evaluation for fitness-for-duty from the Joint Task Force of the American College of Chest Physicians, American College of Occupational Health and Environmental Medicine, and the National Sleep Foundation state that all those wishing to drive a CMV who are suspected of having sleep apnea should be assessed by a sleep physician and have any diagnosis confirmed by overnight polysomnogram (PSG).

Coupled with these recommendations is a growing awareness among physicians and medical examiners of the danger that OSA poses to transportation safety. Together, these factors will increase the demand for access to sleep labs, which will be difficult to satisfy in the face of an acknowledged shortage of testing facilities. This shortfall may lead to delays in diagnosis and treatment initiation. In addition to the deficit in sleep labs, the cost for a PSG is high and may limit access to appropriate testing.(15-17) Consequently, alternative strategies to PSG that can detect and measure the severity of the known risk factors for a crash are actively being considered.

Our aim in addressing Key Question 4 then was to determine whether alternative, low-cost technologies are available that can effectively detect and measure the severity of the known risk factors for a crash among individuals with OSA.

Forty-three articles describing 43 unique studies met the inclusion criteria for Key Question 4. All but one of these studies assessed the diagnostic performance of a portable sleep monitoring system. One study assessed the effectiveness of a clinical model in addition to a portable sleep monitoring system. This study was also the only study to have enrolled only CMV drivers.

The findings of our analyses of the data extracted from the 43 included studies that addressed Key Question 4 are as follows:

- **To date, no model or psychometric instrument has been shown to accurately stratify individuals with OSA by disease severity (a surrogate marker for crash risk).**

- **A number of portable sleep monitoring systems, though not as accurate as the current reference standard (a sleep study in a specialized sleep lab), do offer an alternative method by which the severity of OSA may be assessed in a large number of individuals at a relatively low cost.**
    - **Whether these systems are accurate enough to be considered as acceptable alternatives to the current reference standard for stratifying individuals by OSA severity for the purposes of making decisions about the fitness of an individual to drive a CMV is not clear. Addressing this issue requires that a formal decision and cost-effectiveness analyses be performed. Such analyses are beyond the scope of this evidence report.**

To date, no randomized controlled trial (RCT) has been published that compares OSA-related outcomes known to be associated with driver safety among individuals with OSA who were stratified into risk groups using PSG or an alternative diagnostic test. Consequently, one must attempt to estimate the likely consequences of replacing standard PSG with cheaper, more easily accessible portable sleep monitoring systems using indirect methods. The first stage in this process is to obtain accurate estimates of the diagnostic performance characteristics of available systems. Once such estimates are identified, a decision model needs to be developed into which these diagnostic performance data can be integrated along with other necessary data (e.g., the costs associated with each diagnostic decision option, the prevalence of severe OSA in the United States CMV driver population).

While no portable sleep monitoring system was as accurate as the reference standard (none had a sensitivity and specificity of 100%), our analyses found that the diagnostic performance characteristics of most portable systems were reasonable. That is, the vast majority of available systems could differentiate individuals with OSA from those without, and they could differentiate individuals with severe OSA from those with mild-to-moderate disease better than would be expected by chance alone.

Although we have synthesized the diagnostic performance characteristics of Level II, Level III, and Level IV sleep monitors, we caution the reader that the precision of these estimates is low. While the quality of the included studies was moderate-to-high and the quantity of available evidence was reasonably large, a great deal of heterogeneity in the findings of different studies was observed, even when the tests were performed at the same threshold of OSA severity. Attempts to model this heterogeneity were unsuccessful, and none of the more obvious covariates, such as differences in the device used, the setting in which the study was performed (lab or at home), or the availability of a technician, appeared to be associated with diagnostic performance differences. Indeed, homogeneity testing of diagnostic performance data extracted from studies that used the same device at the same threshold was also found to be heterogeneous.

It is not clear whether currently available portable sleep monitoring systems are accurate enough to be considered as acceptable alternatives to the current reference standard for stratifying individuals by OSA severity for the purposes of making decisions about the fitness of an individual to drive a CMV. Addressing this issue requires that a formal decision and cost-effectiveness analyses be performed. Such analyses, though time consuming and expensive, are central to any decision or policy-making program and fall within the purview of FMCSA's Analysis Division.

Key Question 5: Which treatments have been shown to effectively reduce crash risk among individuals with OSA (as determined by crash rates or through indirect measures of crash risk)?

The overall findings of all of our analyses for Key Question 5 are summarized in Table 2.

Table 2. Summary of Findings – Key Question 5

	Behavioral Modification (weight loss)	CPAP	Dental Appliances	Medications				Surgery		
			Mandibular Advancement Splints	Theophylline	Modafinil (or armodafinil) as Adjunct to CPAP	Mirtazepine	Salmeterol	UPPP	LAUP	TCRFTA
Crash	No evidence	⬤ ***	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Simulated Driving	No evidence	⬤ **	⬤ *	⬤ *	No evidence	No evidence	No evidence	⬤ *	No evidence	No evidence
AHI	⬤ *	⬤ ***	⬤ *	⬤ ?	No evidence	⬤ *	⬤ ?	No evidence	⬤ ?	⬤ ?
Cognitive/ Psychomotor Function	No evidence	⬤ ?	⬤ ?	No evidence	No evidence	No evidence	No evidence	⬤ ?	⬤ ?	No evidence
Daytime Sleepiness (ESS)	No evidence	⬤ ***	⬤ ?	No evidence	⬤ ?	No evidence	No evidence	⬤ *	⬤ ?	⬤ ?
Daytime Sleepiness (MSLT)	No evidence	⬤ ?	No evidence	No evidence	⬤ ?	No evidence	No evidence	No evidence	No evidence	No evidence
Daytime Sleepiness (MWT)	No evidence	No evidence	⬤ ?	No evidence	⬤ *	No evidence	No evidence	No evidence	No evidence	No evidence
Oxygen Saturation	⬤ ?	⬤ ***	⬤ *	⬤ ?	No evidence	⬤ ?	⬤ ?	⬤ ?	No evidence	⬤ ?
24-hour Systolic BP	No evidence	⬤ **	No evidence	No evidence	No evidence	No evidence	No evidence	⬤ ?	No evidence	No evidence
24-hour Diastolic BP	No evidence	⬤ **	No evidence	No evidence	No evidence	No evidence	No evidence	⬤ ?	No evidence	No evidence

Technology has a positive impact on this outcome such that crash risk is reduced.

Technology has a negative impact on this outcome such that crash risk is increased.

Neither a positive nor a negative impact on this outcome has been demonstrated.

*** Strength of Evidence = Strong

** Strength of Evidence = Moderate

* Strength of Evidence = Minimally acceptable

? Results equivocal – strength of evidence too weak at present time to draw an evidence–based conclusion (see text for details)

AHI = Apnea-hypopnea index; BP = Blood pressure; CPAP = Continuous positive airway pressure; ESS = Epworth sleepiness scale; LAUP = Laser-assisted uvula palatoplasty; MSLT = Multiple sleep latency test; MWT = Maintenance of wakefulness test; TCRFTA = Temperature-controlled radiofrequency tissue ablation; UPPP = Uvulopalatopharyngoplasty.

Taking all of the findings summarized in the table above into account, we draw the following evidence-based conclusions:

- **Continuous positive airway pressure (CPAP) reduces crash risk among individuals with moderate-to-severe OSA (Strength of Evidence: Strong).**
- **While several other technologies may reduce crash risk among individuals with moderate-to-severe OSA, the available evidence to support this is not convincing. Consequently, we refrain from drawing further evidence-based conclusions pertaining to other available technologies at this time.**

Key Question 6: What is the length of time required following initiation of an effective treatment (determined by Key Question 5) for patients with OSA to reach a degree of improvement that would permit safe driving (as determined by crash rates or through indirect measures of crash risk)?

Our assessment of the evidence pertaining to Key Question 5 demonstrated that the average driver with OSA is at a significantly increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder. Our assessment of the evidence pertaining to Key Question 5 found that CPAP (and perhaps some other technologies) can reduce the increased crash risk associated with OSA. Currently, it is understood that there is little evidence to help advise individuals with OSA as to when driving can be safely restarted after beginning treatment, or whether it is safe to continue driving if treatment is missed for a few nights.

In addressing Key Question 6, we attempted to identify the length of time required following initiation of an effective treatment for individuals with OSA to reach a degree of improvement that would permit safe driving (as determined through indirect measures of crash risk; i.e., driving simulators, cognitive/psychomotor functioning), or to show improvement in the risk factors associated with OSA (i.e., disease severity, daytime sleepiness, SaO_2, blood pressure).

Twenty-four articles describing 24 unique studies met the inclusion criteria for Key Question 6. The findings of our analyses of the data extracted from these studies are as follows:

- **The impact that CPAP has on crash-risk reduction among individuals with OSA can be seen after as little as one night of treatment (Strength of Evidence: Minimally Acceptable).**

  Studies have shown that improvements in simulated driving performance, the severity of disordered respiration, blood SaO_2*, and some (but not all) measures of cognitive and psychomotor performance improve significantly following a single night of treatment. Exactly how many nights of treatment are required until CPAP exerts its maximum benefit is not known, but evidence suggests that this point has been reached prior to two weeks.*

- **It is not clear how long it takes for other available treatments to exert their maximum effects[2] at this time.**

[2] Assuming that other treatment options do have a positive impact on crash risk (an assumption that is as yet unproven).

Key Question 7: How soon, following cessation of an effective treatment (e.g., as a consequence of noncompliance), will individuals with OSA demonstrate reduced driver safety (as determined by crash rates or through indirect measures of crash risk)?

Four articles describing four unique studies met the inclusion criteria for Key Question 7. All four included studies assessed the effects of withdrawal from CPAP. The finding of our analysis of the data extracted from these studies is as follows:

- **Cessation of CPAP leads to a decrease in simulated driving ability and increases in both OSA severity and daytime sleepiness. The rate at which this deterioration occurs cannot be determined; however, this deterioration may occur as soon as 24 hours following cessation of treatment (Strength of Evidence: Minimally Acceptable).**

Preface

Organization of Report

This evidence report contains four major sections: (1) *Background*; (2) *Methods*; (3) *Evidence Synthesis*; and (4) *Conclusions*. These major sections are supplemented by extensive use of appendices.

In the *Background* section, we provide background information about OSA and driving. Also included in the background section is information pertaining to current regulatory standards and guidelines from FMCSA and three other government transportation safety agencies: the Federal Aviation Administration (FAA), the Federal Railroad Administration (FRA), and the Maritime Administration (MARAD). In addition, we summarize equivalent information from three other countries that are generally considered to have well-developed medical fitness programs: Australia, Canada, and the United Kingdom. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature searching, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesis of clinical study results. The *Evidence Synthesis* section of this report is organized by key question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize available data extracted from included studies either qualitatively or, when the data permit, qualitatively and quantitatively (using meta-analysis). Each section in the *Evidence Synthesis* section closes with our conclusions that are based on our assessment of the available evidence. This evidence report ends with a *Conclusions* section that briefly summarizes the answers to each of the questions addressed.

Scope

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate (12% of all occupation-related deaths) in the United States. About two-thirds of fatally injured truck workers were involved in highway crashes. According to the U.S. DOT, there were 137,144 nonfatal crashes involving a large truck in 2005. 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries. 4,932 of all crashes caused 5,215 fatalities.

The purpose of this evidence report is to address several key questions posed by FMCSA. Each of these key questions was carefully formulated by FMCSA so that its answer will provide information to FMCSA necessary for the process of updating its current medical examination guidelines. The key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with OSA at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Key Question 2: What disease-related factors are associated with an increased motor vehicle crash risk among individuals with OSA?

Key Question 3: Given the findings of Key Question 2, are individuals with OSA unaware of the presence of the factors that appear to be associated with an increased motor vehicle crash risk?

Key Question 4: Are there screening/diagnostic tests available that will enable examiners to identify those individuals with OSA who are at an increased risk for a motor vehicle crash?

Key Question 5: Which treatments have been shown to effectively reduce crash risk among individuals with OSA (as determined by crash rates or through indirect measures[3] of crash risk)?

Key Question 6: What is the length of time required following initiation of an effective treatment (determined by Key Question 5) for patients with OSA to reach a degree of improvement that would permit safe driving (as determined by crash rates or through indirect measures[*] of crash risk)?

Key Question 7: How soon, following cessation of treatment (e.g., as a consequence of noncompliance), will individuals with OSA demonstrate reduced driver safety (as determined by crash rates or through indirect measures[*] of crash risk)?

[3] Indirect measures of driver safety include the following: simulated driving, closed course driving, measures of cognitive function, measures of psychomotor function, and daytime sleepiness.

Background

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate (12% of all occupation-related deaths) in the United States (http://www.bls.gov/iif/oshcfoiarchive.htm#2004charts). About two-thirds of fatally injured truck workers were involved in highway crashes. According to the U.S. DOT, there were 137,144 nonfatal crashes involving a large truck in 2005. 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries. 4,932 of all crashes caused 5,215 fatalities (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2005).

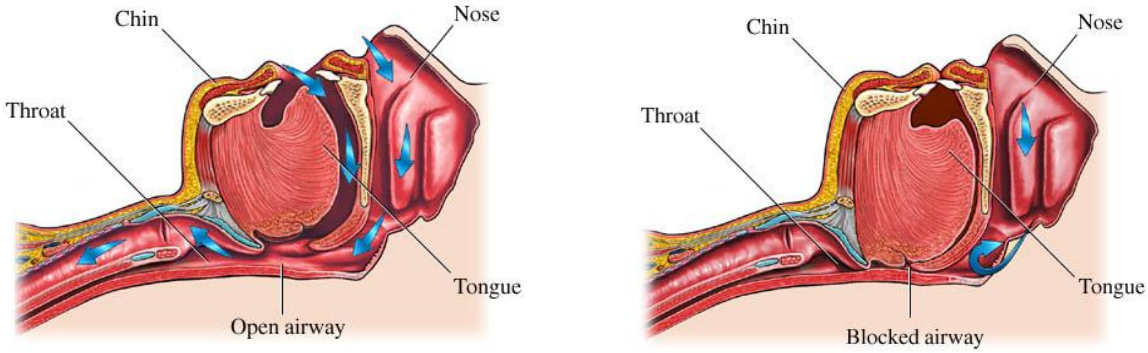
OSA may culminate in unpredictable and sudden incapacitation (e.g., falling asleep at the wheel), thus contributing to the potential for crash, injury, and death. The purpose of this evidence report is to assess and summarize the available data pertaining to the relationship between OSA and motor vehicle crash risk.

OSA

Sleep apnea is a disorder characterized by a reduction or cessation of breathing during sleep coupled with symptoms such as daytime sleepiness (i.e., OSA syndrome).(18-20) It is comprised of two events that take place multiple times during a given period of sleep: apnea, which is a total reduction of airflow for a minimum of 10 seconds with an accompanying effort to breathe; and hypopnea, which is an airflow reduction of at least 50% for a minimum of 10 seconds with a corresponding 4% dip in SaO_2. Together, these events cause a diminution of available oxygen in the bloodstream to which the brain responds by arousing the individual in order to resume breathing, leading to interrupted sleep cycles and daytime sleepiness.(19,21,22) These apneic/hypopneic episodes are often witnessed by family members, especially spouses, who may find their own sleep impacted by their partner's OSA.

OSA occurs as a consequence of repeated upper airway obstruction during sleep as a result of narrowing of the luminal respiratory passages.(20) In normal breathing, air passes through the nasal passages; behind the palate, uvula, and tongue base; through the throat muscles; and between the vocal cords into the lungs (see Figure 1). The muscles of the upper part of the throat keep this passage open to allow air to flow into the lungs. While these muscles usually relax during sleep, the air passage remains sufficiently open to permit the flow of air. Some individuals have a narrower passage (usually at the base of the tongue and palate), and during sleep, relaxation of these muscles causes the passage to close, and air cannot get into the lungs (see Figure 1). Other anatomical variations can act to diminish airflow, including a deviated septum or swollen turbinates (nasal), and a large palate and uvula, which can tip backwards and close the area for breathing. Individuals who sleep on their backs may find that the tongue can obstruct breathing should it fall backwards. Additionally, the side walls of the throat can fall together to narrow or close the airway.

Figure 1. Normal and Obstructed Breathing During Sleep



The U.S. Centers for Medicare and Medicaid (CMS) operationally defines OSA as an AHI of 15 episodes or more per hour of sleep in individuals without sequelae (i.e., high blood pressure, stroke, daytime sleepiness, ischemic heart disease, insomnia, mood disorders—all of which can be caused or worsened by sleep apnea).(23) In individuals with sequelae, OSA is defined as an AHI of five episodes or more per hour of sleep.(23) This definition is more rigorous, because the individual may already be experiencing the negative medical effects of sleep apnea, thus necessitating treatment at a lower AHI.

The International Classification of Sleep Disorders, 2nd Edition (ICSD-2) defines OSA as five or more obstructed breathing episodes per hour of sleep with the appropriate clinical presentation (see Table 3).

Table 3. ICSD-2: OSA in Adults*

A. At least one of the following applies:
   i. The patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, "unrefreshing" sleep, fatigue, or insomnia.
   ii. The patient wakes with breath holding, gasping, or choking.
   iii. The bed partner reports loud snoring, breathing interruptions, or both during the patient's sleep.

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

OR

C. Polysomnographic recording shows at least one of the following:
   i. Fifteen or more scoreable respiratory events (i.e., apneas, hypopneas, or respiratory-effort related arousals) per hour of sleep.
   ii. Evidence of respiratory effort during all or a portion of each respiratory event (in the case of a respiratory-effort related arousal, this is best seen with use of esophageal manometry).

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

Note: For diagnosis, need A, B, and D or C and D.

* from Hartenbaum et al.(23)

The predominant symptom associated with OSA is excessive daytime sleepiness, which is the consequence of poor sleep. Other symptoms associated with OSA include:

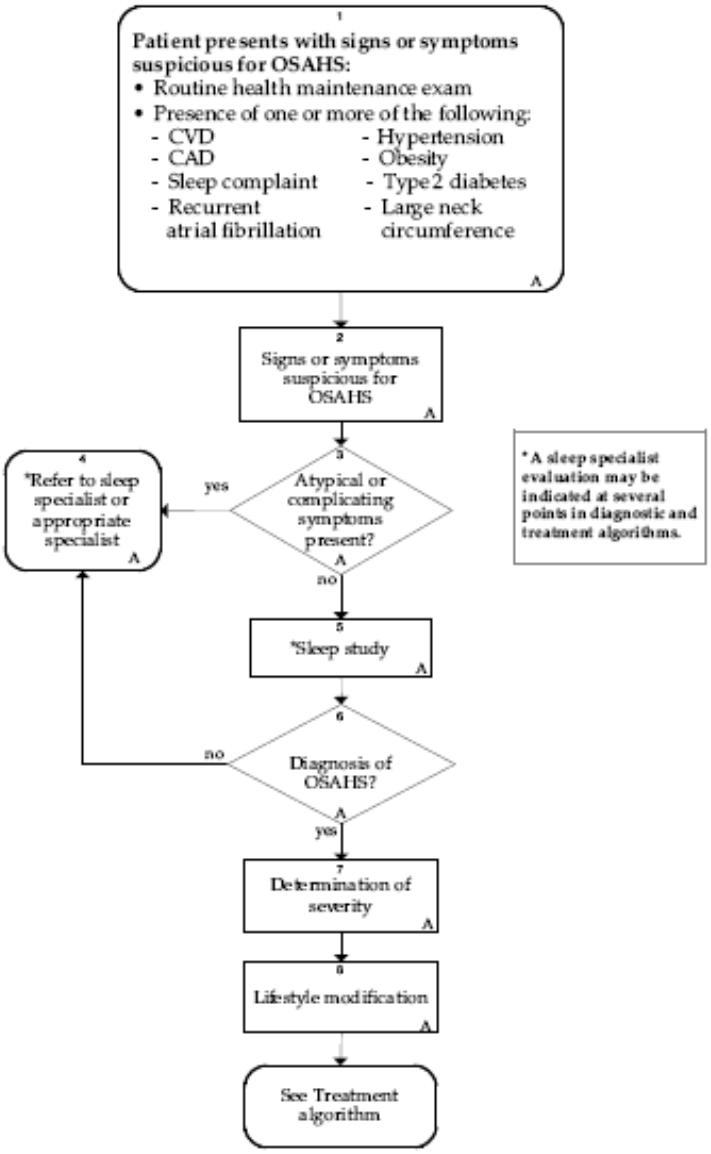
- Loud snoring
- Periods of not breathing (apnea)
- Awakening not rested in the morning
- Dry mouth upon awakening
- Abnormal daytime sleepiness, including falling asleep at inappropriate times
- Morning headaches
- Erectile dysfunction
- Recent weight gain
- Limited attention
- Memory loss
- Poor judgment
- Irritability
- Personality changes
- Depression
- Lethargy

Diagnosis of OSA

A diagnosis of sleep apnea presents some difficulty, as there is a need for standardization of terms and diagnostic criteria. Young et al.(18) found a lack of standardization for even the most basic parameters, such as variable respiratory event requirements. Using symptoms and patient history alone is not adequate in establishing a diagnosis, in part because of the information on individual anatomical details needed to differentiate the potential for sleep apnea versus a diagnosis of another nonapneic sleep disorder.

In an effort to facilitate the diagnosis of OSA, The Institute for Clinical Systems Improvement has created the following algorithm featured in Figure 2.

Figure 2. Diagnostic Algorithm for Adult OSA



CAD = Coronary Artery disease; CVD = Cardiovascular disease; OSAHS = Obstructive sleep apnea hypopnea syndrome.

The gold standard for diagnosing OSA is PSG, also referred to as a sleep study.(24) PSG is a test that measures different physiologic parameters while a subject is asleep. During attended PSG, a technician observes a person sleeping and monitors recording equipment in the setting of a sleep laboratory.
A typical PSG test includes the following(22,24):

- Electroencephalogram (EEG)
- Electro-oculogram (EOG)
- Electromyogram (EMG)
- Oral and nasal airflow measurement

- Chest and abdominal movement measurement
- Audio recording of the loudness of snoring
- Oximetry (blood oxygen levels)
- Video monitoring of the subject

The EEG monitors brain electrical activity and can be used to determine the level of sleep or wakefulness. Electrical activity in the brain during the different stages of sleep is distinctly different from that while awake. The EEG allows the technician and /or physician to determine if the individual is reaching all the stages of sleep to the appropriate depth, and if the individual is being aroused excessively from these stages due to events such as respiratory difficulties or limb movement.

An EOG measures eye movement using electrodes placed near the outer edges of the eyes. During rapid eye movement (REM) sleep (dreaming sleep), the eyes typically move from side-to-side. The EOG measurement of eye movement can help determine when sleep occurs, when REM sleep occurs, and the duration of REM sleep.

An EMG measures muscle movements: with the addition of a monitor placed on the chin, the EMG can also measure muscle relaxation (tone). During stage 1 to 4 of sleep, there is a baseline muscle tone; however, during REM sleep all muscles relax. This difference in tone is noted and recorded by the EMG in order to determine when sleep occurs. The EMG also helps to determine the duration of REM sleep. During PSG, the addition of EMG monitoring of the legs can be used to detect "restless leg syndrome" or periodic leg movements during sleep.

Oral and nasal airflow can be measured by several different methods to help determine the size and frequency of breaths during sleep. *Chest and abdominal movements* occur with each attempt to breathe and can be used to distinguish between central sleep apnea (CSA) and OSA. During CSA, the signal to take a breath is not given, so the muscles do not attempting to take a breath. During OSA, the muscles attempt to take a breath, but no air moves. Respiratory effort and rate help determine and/or confirm a diagnosis of sleep apnea.

Measurement of the *loudness of snoring* can be used to quantify snoring and assist in determining whether sleep apnea may be occurring. Additionally, a measurement is sometimes needed to convince someone that they have a snoring problem. Measurements of loudness of snoring can also be used to measure changes after treatments for snoring.

Oximetry is used to measure the decreases in oxygen in the blood during apneas and hypopneas. It can help establish whether the individual's oxygen levels are unstable, assess individual oxygenation, and help determine the need for supplemental oxygenation.

The *video monitor* is most helpful for detecting movement disorders, parasomnias (sleepwalking, sleeptalking, etc.), or seizures during sleep, particularly in that it allows a review of events with the patient.

After PSG is completed, the data are analyzed by a board-certified sleep specialist. The number of apneas, hypopneas, leg movements, desaturations, and sleep levels are all recorded in a formal report, and a diagnosis is made.

PSG, while the gold standard in sleep apnea diagnosis, may present some difficulties related to access to sleep labs (both in terms of location and time to evaluation) and cost.(23) A study of cost utility on a hypothetical group of individuals by Chervin et al.(1999) found that PSG compared favorably with home

sleep studies and no test (bedside observation), with PSG costing an estimated $4,210 to home study's $3,460 and no test at $3,020 (including follow-up visits, etc.).(25) As anecdotal information, an April 2006 article in the *New York Times* detailed the cost of a PSG at Mt. Sinai Hospital as approximately $1,500.(15-17,26)

Severity Levels in OSA

While OSA is typically stratified in the literature as being mild, moderate, or severe, there appears to be some disagreement as to the most appropriate way to make this stratification. The Institute for Clinical Systems Improvement (ICSI) proposed the following in their March 2007 publication entitled *Diagnosis and Management of Obstructive Sleep Apnea in Adults*:(27)

"Severity is determined by the most severe rating of three domains: sleepiness, respiratory disturbance (AHI), and gas exchange abnormalities (minimum and mean SaO_2)."

According to ICSI, sleepiness can be broken down into three categories: mild (may not be present every day, causes only minor impairment of social or occupational function); moderate (daily sleepiness that occurs when minimally active and moderate degree of attention are required); and severe (daily sleepiness occurring during active tasks or at times where significant attention is needed). Gas exchange abnormalities are also broken down into three categories: mild (mean SaO_2 ≥90%, minimum ≥85%); moderate (mean SaO_2 ≥90%, minimum ≥70%) and severe (mean SaO_2 <90%, minimum <70%).

The prevailing system in the literature for stratifying OSA by severity utilizes the AHI, which is calculated by dividing the number of episodes of apneas or hyponeas by the number of hours of sleep observed.(19,21,22) An estimate of the severity of sleep apnea, or AHI is derived by measuring the episodes of apnea and hypopnea over a two-hour period (preferably across all stages of sleep) and dividing the total number of episodes by the hours of observed sleep.(19,21,22) Under this system, an individual with an AHI of 5 to 15 events per hour is categorized as having mild OSA; an individual with an AHI of 15 to 30 events per hour is categorized as having moderate OSA; and an individual with an AHI of greater than 30 events per hour is categorized as having severe OSA.(22) In another grading scale that utilizes minimum blood oxygen desaturation, mild OSA is defined as a minimum oxygen desaturation of ≥85%; moderate OSA is defined as a minimum oxygen desaturation of 65% to 84%; and severe OSA is defined as a minimum oxygen desaturation of <65%.(22)

Another instrument used to measure sleep apnea is the RDI.(22) The RDI is similar to the AHI; however, it also includes respiratory events that do not technically meet the definitions of apneas or hypopneas, such as snoring arousals, hypoventilation episodes, and desaturation events.

Prevalence and Incidence of OSA

OSA is a relatively common disorder affecting approximately 12 million individuals in the United States, with approximately 4% of men and 2% of women in the United States suffering from symptomatic sleep apnea (i.e., AHI of ≥5 with excessive daytime sleepiness).(18,20,28-30) The American Sleep Apnea Association estimates that there are an additional 10 million individuals with undiagnosed sleep apnea. Current estimates find that 1 in 5 white adults with an average BMI of 25 to 28kg/m has an AHI of ≥5 (mild OSA, minimally symptomatic OSA, or asymptomatic OSA), and that 1 in 15 of these individuals has an AHI of ≤15 (moderate OSA). Worldwide, the prevalence of OSA is believed to be approximately 5% of the adult population (figures are for Western countries only). The prevalence of mild OSA is estimated to be between 3% and 28% of the adult population; for moderate OSA (≥15 AHI) the figures range between 1% and 14%.

The incidence of OSA (the development of new cases over a defined period of time) has been problematic to establish, primarily because of difficulties in identifying individuals who are not affected by OSA and by variability in the indices used to measure the disease, which leads to errors in OSA classification. Studies have, therefore, addressed disease progression rather than disease incidence.(18)

Some populations of individuals are more likely to develop OSA than others:(18,20,28-31)

- Men are more likely to develop OSA than women before age 50. After age 50, the risk is the same in men and women. This is believed to be associated with hormonal influences, particularly because postmenopausal women appear to be more likely to develop the disease than premenopausal women.
- OSA is more common in obese individuals. It is estimated that 70% of individuals with a BMI >25 have OSA. OSA worsens in severity and prevalence with increasing obesity.
- OSA is more common among individuals with cardiovascular disease. It has been estimated that 30% to 50% of such individuals have OSA. Among individuals who have experienced a stroke, the prevalence of OSA may be as high as 60%.
- Ethnicity may play a part in the potential to develop OSA. African-Americans have a 2.5 times greater risk of OSA than Caucasians. In India, 7.5% of the general male population has OSA. Chinese males have a 4% prevalence and Chinese females a 2% prevalence of OSA.

Risk Factors for OSA

The primary risk factor for OSA is excessive weight gain: specifically, the accumulation of fat on the sides of the upper airway causes it to become narrow and predisposed to closure when the muscles relax during sleep.(22,31) Medical examiners for the certification of CMV drivers are also encouraged to observe the neck circumference (NC), as it has been linked to BMI and an increased risk of OSA.
Other prominent risk factors for the development of OSA include age and male gender, although the correlation between increasing age and increased prevalence of sleep apnea has been contested in reviews such as Young et al.(18) It is also postulated that male hormones can cause structural changes in the upper airway that may be related to the eventual development of OSA. Conversely, the lack of solid data illustrating a hormonally linked increase in OSA rates among menopausal women has raised some doubts about hormone changes as a risk factor for OSA development.(18) Other predisposing factors associated with the development of OSA include:

- Anatomic abnormalities, including a receding chin, narrow airway, and certain shapes of the palate and jaw
- Enlarged tonsils and adenoids (the main causes of OSA in children)
- Family history of OSA, although no genetic inheritance pattern has been proven
- Alcohol and sedative drugs use, which relax the musculature in the surrounding upper airway
- Smoking, which can cause inflammation, swelling, and narrowing of the upper airway
- Diseases and conditions, including: hypothyroidism, acromegaly, renal failure, amyloidosis, vocal cord paralysis, post-polio syndrome, neuromuscular disorders, Marfan's syndrome, and Down syndrome
- Nasal obstruction
- Large tongue

Screening for OSA

Screening for OSA presents several challenges to the medical examiner. In the absence of PSG and patient history, self-reported symptoms and anthropometric measurements often must serve as the primary way of discerning whether an individual has developed OSA. While this system demonstrates high sensitivity (>80%), it also has a low specificity (<60%). This means that individuals with sleep apnea have a reasonable chance of being correctly diagnosed with the disorder, but that individuals without OSA who are being screened have a definite possibility of being misidentified as having the disorder.(18) In addition, the utility of the instruments is only as good as the information it records – if the data given are not correct, the accuracy of the results will suffer. The motivation to misrepresent symptoms and severity would certainly increase with the likelihood that a diagnosis of OSA would mean loss of employment. Ideally, considering the cost and waiting time associated with PSG, accurate screening tools would rely less on self-report and more on easily, precisely, and economically measured data to establish a diagnosis of OSA.

Specific screening models for OSA based on various combinations of clinical symptoms, physical examinations, demographics, and anthropometric parameters have been used to predict the presence or absence of OSA in a given patient.(32) These models may have clinical utility for patients in whom OSA is suspected as *a screening tool* to help clinicians to decide which patients should be referred to sleep centers for further testing. Most of the models included the following variables: gender, BMI, NC, cephalometry measurements, home oximetry, and ESS score. However, these prediction models do not assess the severity of OSA. PSG or evaluation with portable monitoring is still necessary to distinguish patients with mild cases of OSA and those with severe cases.(33)

Two examples of such screening models are presented below:

- A predictive model based on clinical variables, physical examination, pulse oximetry, and imaging techniques was expressed as follows:

  P (OSA/gender, NC, dips, Epworth, Go-GN)

  The independent predictors of OSA were NC, gender, and cephalometric index (Go-GN), desaturation (dips), and ESS score.(32)

- Another model that combined measurements of the oral cavity with BMI and NC was expressed as follows:

  P+ (Mx-Mn) 3× OJ +3× [max (BMI – 25, 0] × (NC ÷ BMI)

  Where P is palatal height; Mx, Mn, and OJ are measurements of the oral cavity; BMI is the body mass index, and NC is neck circumference.(33)

Other screening tools to better select patients for PSG include: radiologic imaging of the head and neck for anatomic abnormalities predictive of OSA (including cephalometry), anthropometric measurements, such as NC and focused questionnaire, including the Berlin Questionnaire, the ESS, the Multivariate Apnea Detector questionnaire, and the Functional Outcomes of Sleep Questionnaire. Drawbacks associated with PSG as a screening tool are detailed in the subsection of this report entitled "Diagnosis of Obstructive Sleep Apnea."

Health Consequences of OSA

OSA has been accepted as a clinical diagnosis for approximately 30 years, yet an understanding of the potential health consequences has been largely ignored.(18) Untreated OSA increases the risk of the following disorders:(18-22,29-31,34)

- Excessive daytime sleepiness (EDS)
- Hypertension
- Angina
- Right-sided heart failure (cor pulmonale)
- Myocardial infarction
- Arrhythmias, including severe bradycardias
- Dilated cardiomyopathy
- Excessive carbon dioxide levels (hypercapnia)
- Diabetes
- Stroke
- Sudden death

Sleep apnea is considered an important risk factor for hypertension and heart problems (independent of other risk factors such as excess weight), primarily by promoting a series of reactions that create an increase in stress on the heart during the night.(18) As outlined in the beginning of the *Background* section, apneic/hypopneic episodes create a decrease in SaO_2: as the episodes continue, the sympathetic nervous system response ("fight or flight") is activated. Nerve and adrenaline signals cause the blood vessels to constrict in an effort to deliver more blood and oxygen to the brain and muscles; in order to fulfill this function, the heart activity increases, and blood pressure subsequently increases. Combined with the signal for the heart to work harder and lower available oxygen in the blood, this increase in blood pressure creates increased stress on the heart throughout the night, which is precisely the time when demand on the heart should be lessened. Ultimately, 45% of individuals with mild OSA who do not currently have hypertension will develop the disorder within four years of diagnosis. An estimated 80% of individuals who are using more than one medication to control hypertension have OSA. Lastly, it has been observed that treatment of OSA is related to a decrease in high blood pressure.

OSA is associated with a number of other cardiovascular problems, including congestive heart failure (risk is increased by 2.3) and risk of stroke (risk is increased by 1.5). It is also associated with complications in the treatment of atrial fibrillation, a condition in which the upper part of the heart (atrium) is beating out of coordination with the lower part (ventricle). In individuals who undergo cardioversion to treat atrial fibrillation, 50% experience a recurrence of the condition; individuals with OSA experience an 80% recurrence rate.

Relationship between OSA and Excessive Daytime Sleepiness

While sleep deprivation due to excessive driving hours is probably the single most important cause of driver sleepiness, sleep disorders (such as OSA) are thought to account for a significant number of sleep-related crashes due to excessive daytime sleepiness (EDS).

Causes of EDS range from insufficient or inadequate sleep to drug effects and sleep disorders, such OSA.(35) The prevalence of EDS ranges from 3% to 23% of the general U.S. population.(35-37) The consequences of EDS can be significant, including crashes, negative economic and public health outcomes, reduced work and school performance, and impaired psychosocial functioning.(36)

A study of long-haul truck drivers by Souza et al. (2005) found that 47% had fallen asleep at the wheel while driving.(36) Published estimates of the proportion of crashes attributable to sleepiness vary more than tenfold, from 1% to 3% for the United States to 10% in France and over 30% in Australia.(37-39) The U.S. National Highway Traffic Safety Administration (NHTSA) estimates that sleepiness is the primary causal factor in 100,000 police reported crashes each year, resulting in 76,000 injuries, 1,500 deaths(39,40), and an estimated monetary loss of approximately $12.5 billion each year.(39) Given the number of people with EDS and the potential outcomes, it is important that physicians, educators, and public policy makers approach this complaint thoughtfully.

Treatments for OSA

There are a variety of treatments for OSA, which are subject to an accurate diagnosis derived from an individual's medical history, the severity of the disorder, and the specific cause of the obstruction. These treatments involve lifestyle changes, such as avoiding alcohol and medications that relax the central nervous system (i.e., sedatives, muscle relaxants); weight loss; smoking cessation; the use of special pillows or devices to prevent an individual from sleeping on his/her back; or oral appliances that function to keep the airway open during sleep.

If these conservative methods are inadequate, physicians often recommend CPAP. To administer CPAP, a face mask is attached to a tube and a machine blows pressurized air into the mask and through the airway to keep it open. There are also surgical procedures that can be used to remove and tighten tissue and widen the airway. Some individuals may need a combination of therapies to successfully treat their sleep apnea. In this section we describe a variety of nonsurgical and surgical treatments for OSA.

Nonsurgical Treatments

The nonsurgical treatments for OSA are similar to the nonsurgical treatments for snoring. Nonsurgical treatments include the following:

- Behavior modification
- CPAP
- Dental appliances
- Pharmacotherapy

Behavior Modification

Behavior modification is the simplest of treatments for mild OSA, but often the hardest to make. For some individuals, the behavior to be modified is sleeping position, as apneas will occur in conjunction with, or be exacerbated by, certain sleep positions such as lying on the back. Positional therapy can be used to treat patients whose OSA is related to body positioning during sleep.(41) Strategies associated with positional therapy include sewing or attaching a sock filled with tennis balls length-wise down the back of an individual's pajama top or nightshirt. This creates discomfort for the individual when they attempt to lie on their back such that the sleeper will usually move onto their side. Another technique involves the use of positional pillows to assist in sleeping on the side. Positional therapy, while not

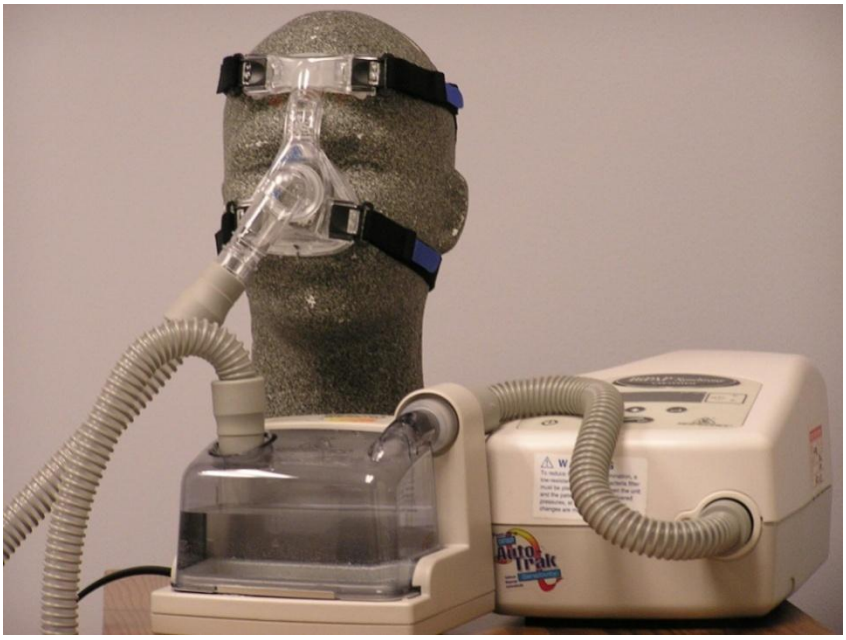
effective in all cases of OSA, has met with success in some patients. In addition to therapies specifically aimed at sleep behavior, changing behavior so that an individual avoids alcohol, smoking, and certain medicines may alleviate mild OSA.(41)

Weight gain is a significant risk factor for the development OSA. Therefore, a healthy lifestyle and diet that encourages weight loss will help improve OSA.(41) Unfortunately, most people with OSA are tired and do not have much energy for exercise. This is a difficult behavioral spiral since the more tired a person is -- the less they exercise -- the more weight they gain -- the worse the OSA becomes -- and the more tired they become. After OSA is treated by other methods, people are frequently able to lose weight, and OSA improves.

Continuous Positive Airway Pressure (CPAP)

In finding a treatment for OSA, the primary goal is to hold the airway open so it does not collapse during sleep. Currently the most common treatment for OSA at any level is CPAP.(24) CPAP uses air pressure to hold the tissues open during sleep by delivering air through a nasal mask or face mask held in place by Velcro straps around the patient's head (see Figure 3). As the individual breathes, the positive pressure holds the nose, palate, and throat tissues open and blows heated, humidified air through a short tube connected to a small air compressor. The mask must be worn snugly to prevent the leakage of air: to accommodate different needs, there are many different masks, including nasal pillows, nasal masks, and full-face masks. The CPAP machine is portable.

Figure 3. CPAP Machine



With CPAP it is important to use the lowest possible pressure required to keep the airway open during sleep. This pressure is determined by "titration," a process in which a technician monitors the sleeping patient for apneas and hypopneas during PSG, and then adjusts the air pressure until the apneas/hypopneas decrease to a normal level or are eliminated altogether. A different pressure may be needed for different positions or levels of sleep. The lowest pressure needed to control OSA in all positions and sleep levels is then prescribed.

People with mild-to-moderate OSA often have more compliance issues with CPAP therapy when compared to individuals with severe OSA. Approximately 60% of individuals with mild to moderate OSA report that they use their CPAP machines, but when use time is measured only 45% to 55% of these individuals actually use CPAP for more than 4 hours per night.(24) Between 25% and 50% of people who start using CPAP discontinue the therapy due to feelings of claustrophobia induced by the use of the mask. Some individuals find that using the mask, or having to take it with them during travel, is an inconvenience and forgo further therapy. Others do not like the image of having to sleep with a mask. Some individuals discontinue CPAP use due to side effects such as contact dermatitis, skin breakdown, mouth leaks, nasal congestion, runny nose (rhinorrhea), dry and/or sore eyes, headaches, nose bleeds (rare), tympanic membrane rupture (very rare), chest pain, difficulty exhaling, pneumothorax (very rare), smothering sensation, and excessive swallowing of air (aerophagia).

Bi-level positive airway pressure (BiPAP) is a variation of CPAP that was designed for people who do not tolerate the higher pressures of CPAP.(24) It is similar to CPAP in that a machine delivers a positive pressure to a mask during sleep. Because the air pressure required to prevent respiratory obstruction is typically less on expiration than on inspiration, the BiPAP machine delivers a higher pressure during inspiration, and a lower pressure during expiration, which allows for more comfortable breathing. BiPAP was designed to improve CPAP compliance; however, it has proven difficult to measure an increase in compliance when compared to standard CPAP. BiPAP is often only approved by insurance companies after documentation that a patient cannot tolerate CPAP.

The auto-titrating CPAP machine represents a new development in sleep apnea treatment. These "smart" CPAP machines are designed to provide the minimum necessary pressure at any given time and to automatically adjust that pressure as the needs of the patient change throughout the night.(24,42) As discussed previously, different pressures are required to effectively accommodate different levels of sleep and positions. At a given pressure, if a person starts to have an apnea or hypopnea, the machine adjusts the pressure higher until the episodes are controlled.(42) If a person is in a sleep level or position that doesn't need a higher pressure, the pressure is reduced. This ability to adjust air pressure may help to overcome the effects of weight gain or alcohol or sedative use, and may assist in achieving compliance with CPAP therapy. The flexibility of the auto-titrating CPAP means that the minimum pressure required to reduce or eliminate apnea/hypopnea episodes is maintained. However, if the machine does not make the appropriate adjustment, the air pressure may be too high for comfort or too low to prevent or decrease apnea/hypopnea events.

Dental Appliances

Dental appliances focus on moving the tissues of the airway to allow for normal breathing. Specifically, a dental appliance functions to hold the jaw and tongue forward and raise the palate, thus preventing closure of the airway. This small increase in airway size often is enough to control the apneas. Dental appliances used for the treatment of OSA generally come in two categories: mandibular advance devices and tongue-retaining devices.(24,43)

Mandibular advance devices consist of a plastic (or other material) mold of the teeth, and may be said to most closely resemble the athletic mouth guards commonly used in boxing, football, and other contact sports.(44) The mold for the lower teeth is advanced further forward than the mold for the upper teeth, thus moving the mandible forward, opening the airway, and preventing its collapse during sleep.(44) It is effective in mild cases of OSA, particularly if the patient's OSA is positional.

Tongue-retaining devices resemble an athletic mouth guard, and are placed between the upper and lower teeth. The device acts like a suction cup in which the tongue sits in the suction device and is pulled forward during the night.(24,43,44) Positioning the tongue forward may eliminate any obstruction caused by the base of the tongue.

Advantages to the use of the dental appliance include the fact that it does not require surgery; it is small and portable; and it does not need machinery. However, there are some disadvantages to the dental appliance. It can cause or worsen temporomandibular joint (TMJ) dysfunction. If the jaw is pulled too far forward, it can cause pain in the joint when eating.(24,43,44) For this reason, it is best to have a dentist or oral surgeon fit and adjust the appliance. A dental appliance requires natural teeth to fit properly. The appliance must be worn every night. The cost is variable, as is insurance coverage.(44)

Medications

Many medications have been suggested as potential therapies for OSA; however, because OSA is due to an anatomic airway narrowing, it has been difficult to find a medication that provides a genuine therapeutic benefit.

Individuals with OSA caused by nasal airway obstruction have effectively used nasal steroid sprays and topical nasal decongestants such as oxymetalazone and neosynephrine to temporarily improve nasal swelling and treat the OSA symptoms. These solutions are only temporary (three to five days), however, due to issues of decreased effectiveness and withdrawal symptoms.

Individuals who have OSA secondary to hypothyroidism (low thyroid hormone production) experience improvement with thyroid replacement therapy. Individuals with normal thyroid functions do not experience any improvement in OSA.

Those individuals with OSA secondary to obesity may achieve an improvement in OSA symptoms with the use of diet medications, provided the therapy helps them achieve weight loss.

Other medications that have been studied, including medroxyprogesterone (Provera, Cycrin, Amen), acetazolamide (Diamox), theophylline (Theo-Dur, Respbid, Slo-Bid, Theo-24, Theolair, Uniphyl, Slo-Phyllin), tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs), demonstrated little or no effect in treating OSA. New medications to help increase alertness, such as modafinil (Provigil) have been shown to be temporarily successful in increasing attention. However, they do not treat the cause of OSA or attendant sleep deprivation.

Surgical Treatments

There are several surgical options available to treat OSA: the type of surgery that is chosen is dependent on an individual's specific anatomy and severity of sleep apnea. To many individuals, surgery promises a cure with a single treatment, and does not have the attendant difficulties associated with behavior modification or CPAP therapy. Surgery, however, carries it with a small risk of adverse events, requires time off from work to heal, and individuals who undergo surgery may have post-operative pain for up to three weeks after surgery. Some of the potential general risks of surgery include:

- bleeding;
- infection;
- formation of scar tissue;
- pain;

- loss of work;
- change in voice;
- problems swallowing;
- failure to cure sleep apnea;
- anesthesia risks (including allergic reaction, stroke, heart attack, and death); and
- other unforeseen surgical complications.

Surgical therapy is generally considered only after all the risks, benefits, and alternatives are understood by the patient. In keeping with this philosophy, many insurance companies require a three-week trial of CPAP treatment before authorizing surgery for sleep apnea. Given that CPAP, if tolerated, controls most sleep apnea, the nonsurgical option may be better than the available surgical options due to the nature of the adverse events associated with CPAP when compared to the adverse events associated with surgery.

Any surgical treatment for sleep apnea must address the anatomical "problem areas": those areas which function to compromise airflow and cause apnea. Surgical treatments can address the nose, palate, tongue, jaw, neck, obesity, or several of these areas at the same time. Each surgery's success rate is determined by whether or not a specific airway collapse is prevented. Therefore, the ideal surgery is different for each patient and depends on each patient's specific problem. Common surgical options for individuals with OSA include the following:

- Nasal airway surgery
- Palate implants
- Uvulopalatopharyngoplasty (UPPP)
- Tongue reduction surgery
- Genioglossus advancement
- Hyoid suspension
- Maxillomandibular procedures
- Tracheostomy
- Bariatric surgery

Many individuals with OSA have several sources of airway obstruction. As a consequence, these surgical options are frequently performed together. For example, UPPP is often performed in conjunction with genioglossus advancement and hyoid suspension.

Nasal Airway Surgery

The nasal cavity can be obstructed by swelling of the turbinates, septal deviation, and nasal polyps. Surgeries to address each of these potential causes of obstruction can improve air flow through the nasal passages. Because nasal obstruction makes CPAP difficult or even intolerable, nasal surgery is sometimes used in individuals with OSA to improve the tolerability and effectiveness of CPAP.

Palate Implants

Palate implants serve to stiffen the palate to prevent the pharyngeal collapse associated with OSA.(45) This procedure is performed in a physician's office using local anesthesia. It involves implanting three small, woven inserts into the soft palate to help support and improve the structure of the palate and prevent it from collapsing and obstructing the airway. Palatal implants also decrease the vibrations of the palate that cause snoring. Complications of the therapy are rare and include partial extrusion, which involves seeing or feeling the tip of the insert through the surface of the soft palate. The inserts used can be removed and/or replaced easily by a physician.

UPPP

UPPP is the most common surgical procedure for treating individuals with OSA. UPPP prevents the collapse of the palate, tonsils, and pharynx, which is common in OSA. Hence, it is most successful in patients who have large tonsils, a long uvula, or a long, wide palate. It also is more successful in patients who are not obese.

UPPP surgery involves the removal of part of the soft palate, uvula, and redundant peripharyngeal tissues, sometimes including the nostrils.(46) The procedure usually requires an overnight stay in the hospital to monitor breathing and control pain, with significant postsurgical discomfort for approximately two weeks. Complications of UPPP include transient nasal reflux, nasal speech, minor loss of taste, and tongue numbness. More significant, and infrequent, complications include permanent nasal reflux velopalatal insufficiency and changes in the person's voice and palatal stenosis, which can make OSA worse. Approximately 1% of individuals who undergo UPPP experience bleeding in the area of the tonsils for up to 10 days after surgery: occasionally, a second operation is needed to stop this post-operative bleeding. Some individuals who achieve a "successful UPPP" and fewer episodes of apnea still require the use of CPAP therapy after surgery to completely control their OSA.

Tongue Reduction Surgery

In some people with OSA, the area of collapse is between the base of the tongue and the back wall of the throat (pharynx). Several surgical techniques have been used to decrease the size of the base of the tongue and open the airway in order to alleviate OSA symptoms. Most of these procedures are performed as an adjunctive treatment to other surgical procedures. The two procedures covered in this subsection are laser midline glossectomy and radiofrequency ablation (RFA).

Laser midline glossectomy serves to relieve OSA by decreasing the size of the tongue. This is achieved by using a laser to cut a trough down the middle of the base of the tongue. The special challenge to this is removing enough tissue to prevent collapse without changing the natural functions of the tongue during speaking and swallowing. Laser midline glossectomy is often used for people who have undergone UPPP but continue to have OSA.

RFA is a surgical procedure designed to shrink the base of the tongue through the creation of scar tissue at the site. The first treatment, in which the radiofrequency probe is placed in the muscle of the back of the tongue and energy is delivered to create controlled damage, is usually performed under general anesthesia. Over time, the damaged tissue scars and shrinks. Remaining treatments can be performed in an office. Adverse events associated with RFA include the development of an infection or abscess in the tongue, which can narrow the airway and may require further surgery.

Genioglossus Advancement

The genioglossus muscle is the muscle that attaches the base of the tongue to the inside front of the jaw bone. The genioglossus pulls the tongue forward. In individuals with OSA, it has been demonstrated that the genioglossus is more active in holding the airway open at rest. When this muscle relaxes during sleep, the airway narrows and collapses.

There are a several procedures that pull the tongue forward to enlarge the airway. A genioglossus advancement typically detaches the part of the jaw bone where the muscle attaches and moves it forward about 4 mm. This pulls the base of the tongue forward. Genioglossus advancement is performed under general anesthesia and requires cutting the bone and screwing it back in place. This usually is performed in combination with hyoid suspension or UPPP.

Other less invasive methods are available to advance the genioglossus muscle. One method uses a stitch through the base of the tongue that attaches to a screw on the inside of the jaw. While the method may be less invasive, it may also prove to be less effective and less permanent.

Hyoid Suspension

The hyoid bone helps support the larynx and tongue in the neck. It is located inferior to the mandible and tongue, superior to the laryngeal cartilages, and is not directly attached to any other bones, but to strap muscles above and below. The strap muscles serve to elevate or depress the larynx during swallowing.

As part of a surgical procedure to bring the tongue and soft tissues up and forward, the hyoid bone may be suspended by being sutured close to the mandible. Hyoid suspension is rarely performed as a sole surgical option, but usually functions as an adjunct treatment to surgical procedures such as UPPP or genioglossus advancement.

Maxillomandibular Advancement

Maxillomandibular advancement is a surgical procedure that moves the jaw and upper teeth forward in order to pull the palate and base of the tongue forward and open the airway. The mandible and maxillary bones are cut, moved forward, realigned, and plated into place. Care must be taken to keep the teeth aligned and preserve a normal bite, and to preserve the nerve that supplies sensation to the front teeth and lip. Therefore, the procedure usually is performed by an oral surgeon.

Tracheostomy

Tracheostomy (a procedure used to bypass the narrowed airway) is the oldest surgical treatment for OSA still used as a therapeutic option, albeit rarely. It is generally reserved for morbidly obese patients with severe OSA who are not candidates for other treatments. The tracheostomy functions to treat airflow obstruction that occurs above the larynx by allowing airflow directly into the trachea by the insertion of a plastic or metal tube into the trachea.(41) The tube remains capped during the day to allow for normal voice use and breathing through the nose and mouth, and is then opened at night to bypass the obstructed area.

A tracheostomy can be a temporary procedure, and is kept in place only as long as it is needed. The tube is generally easy to remove, and the wound is usually quick to heal. Tracheostomy has close to a 100% rate of cure for OSA, because it bypasses the problem in the upper airway. In mixed sleep apnea,

obstructive apneas resolve immediately, but central apneas, which are due to metabolic changes caused by the obstructive apneas, usually take some time to resolve.

As with all surgical procedures, there are risks and complications associated with tracheostomy. The first is a psychosocial problem: people do not want to appear in public with a visible tracheostomy tube. Secondly, the tracheostomy hole requires maintenance, and must be cleaned daily. Adverse events associated with a tracheostomy include the development of local infections or scar tissue around the inside or outside of the hole. Individuals can develop recurrent infections in the bronchi. Should the tube erode into a major blood vessel in the neck, severe, life threatening bleeding may occur, although this is a rare complication of this treatment. The trachea may stay narrowed at the tracheostomy site after the tube is removed, necessitating further surgery.

Bariatric Surgery

Bariatric (obesity) surgery is a new type of surgical therapy for OSA. It is effective because most sleep apnea is caused by or worsened by obesity, and bariatric surgery is associated with a marked post-operative reduction in weight. Bariatric surgery is only considered an option for morbidly obese patients with severe OSA, and it carries a 10% morbidity rate as well as a 1% mortality rate.(45) Because patients can regain the weight they lost after surgery, it is not a "perfect cure" for severe sleep apnea in the morbidly obese.(45) Bariatric surgery, like the other surgical procedures that have been discussed, has significant risks and is not suitable for most patients with OSA.

Commercial Drivers and OSA

In the United States, approximately 5,600 people are killed annually in crashes involving CMVs.(47) Between 20% and 30% of crashes involving CMV drivers are sleep related.(48)

Dr. Allan Pack and colleagues at the University of Pennsylvania recently published one of the largest and most comprehensive epidemiologic studies on the prevalence of OSA in CMV drivers produced to date.(47) To measure the impact of fatigue on driver performance and safety, they sent questionnaires to 4,826 drivers who had CMV licenses and lived within 50 miles of the University of Pennsylvania sleep centers. After getting complete responses from 1,329 drivers, they focused on 247 drivers at high risk for sleep apnea and 159 drivers at low risk. They found that 28% of CMV drivers have OSA[4] (i.e., 7 times more than the general population), with nearly 5% of them having severe OSA[5].

Technologies to Monitor Drivers for Excessive Sleepiness[6]

Driver sleepiness has long been recognized as a problem in the trucking industry. The federal hours of service rules (first imposed in 1938) are an attempt to control the problem of sleepy drivers through regulation and enforcement. However, even strict adherence to the hours of service regulations is not a guarantee that a driver will not become sleepy sometime during the course of a long shift.

[4] Defined as an AHI ≥5 episodes per hour

[5] Defined as an AHI ≥30 episodes per hour

[6] Source of information from http://www.fmcsa.dot.gov/facts-research/research-technology/publications/pilot-test/fmt-selected-for-study.htm

In an effort to combat the problem of sleepy drivers a number of technologies have been developed. These technologies fall into two broad categories; those that measure performance through vehicle-based monitoring and those that measure performance through driver-based monitoring.

In April of 2005, FMCSA conducted a study titled, "Pilot Test of Fatigue Management Technologies" (Report No. FMCSA-RT-05-002) as part of a project to determine which, if any, available technologies showed promise in improving alertness and drivers' awareness of how sleepy they are, as well as to determine drivers' reactions and acceptance of these technologies.

Three commercially available technologies for the management of sleepiness were assessed in the study. Two of these technologies monitored drivers and one technology monitored the vehicle. The first driver-based device, called SleepWatch® (developed by Walter Reed Army Institute of Research and marketed by Precision Control Design of Fort Walton Beach, FL, USA), is worn like a watch and monitors rest and activity patterns. Based on those patterns it provides feedback to the driver concerning performance levels and the need for sleep.

The second driver-based device, called the Copilot® (marketed by Attention Technologies of Pittsburgh, PA, USA), is a dashboard-mounted unit approximately the size of a small digital camera. It uses infrared-based retinal scanning to determine how often a driver blinks and how long his/her eyes stay shut. The device beeps to provide drivers immediate warning as they approach a dangerous level of drowsiness.

The vehicle-based technology, called SafeTRAC® (manufactured by Applied Perception and AssistWare Technology of Wexford, PA, USA), is a lane-tracking system that uses a small camera connected to a microprocessor. The system monitors the position of the vehicle in the driving lane and detects drifting, weaving, or tracking irregularities and provides both visual and audible feedback to the driver.

All three technologies tested by FMCSA appeared to have beneficial effects as far as improving alertness and drivers' awareness of sleepiness. However, feedback from the drivers at the end of the project indicated that they prefer devices that monitor the truck as opposed to those that monitor the driver. Many of the drivers expressed concerns about the privacy of the data generated by devices that are designed to monitor them as opposed to their vehicles, particularly as all of these devices generate information that can be stored and retrieved at a later time by individuals such as employers or police, or by organizations such as courts and insurance companies.

Current Medical Fitness Standards and Guidelines for CMV Drivers in the United States

Current Medical Fitness Standards

The current medical qualification standard for fitness to drive a CMV (49 CFR 391.41(b) subpart 5) states the following (see: http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrruletext.asp?section=391.41):
A person is physically qualified to drive a CMV if that person —

- Has no established medical history or clinical diagnosis of a respiratory dysfunction likely to interfere with his/her ability to control and drive a CMV safely.

Current Medical Qualification Guidelines

In 1988, FMCSA published the outcome of a conference to review the current medical standards covering neurologic disease (see: http://www.fmcsa.dot.gov/facts-research/research-technology/publications/medreports.htm), which included guidelines for patients with SAS. Unlike standards that are regulations that a medical examiner must follow, these guidelines are recommendations that the medical examiner should follow. While not law, the guidelines are intended as standards of practice for medical examiners.

Current FMCSA guidelines pertaining to SAS state:

"Patients with SAS having symptoms of excessive daytime somnolence cannot take part in interstate driving, because they likely will be involved in hazardous driving and crashes resulting from sleepiness. Even if these patients do not have the sleep attacks, they suffer from daytime fatigue and tiredness. These symptoms will be compounded by the natural fatigue and monotony associated with the long hours of driving, thus causing increased vulnerability to crashes. Therefore, those patients who are not on any treatment and are suffering from symptoms related to EDS should not be allowed to participate in interstate driving. Those patients with SAS whose symptoms (e.g., EDS, fatigue) can be controlled by surgical treatment (e.g., permanent tracheostomy) may be permitted to drive after 3-month period free of symptoms, provided there is constant medical supervision. Laboratory studies (e.g., polysomnographic and multiple sleep latency tests) must be performed to document absence of EDS and sleep apnea."

Medical Fitness Standards and Guidelines for Individuals Performing Transportation Safety in the United States

Current medical fitness standards and guidelines for individuals performing transportation safety in the United States are summarized in Table 4. Included in the table are pertinent rules and guidance for pilots, railroad workers, and merchant mariners.

Table 4. Standards and Guidelines for Sleep Apnea from U.S. Government Transportation Safety Agencies

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
Sleep Apnea	Examiners may reissue an airman medical certificate under the provisions of an Authorization, if the applicant provides the following: • An Authorization granted by the FAA. • A current report (performed within last 90 days) from the treating physician that references the present treatment, whether this has eliminated any symptoms and with specific comments regarding daytime sleepiness. If there is any question about response to or compliance with treatment, then a Maintenance of Wakefulness Test (MWT) will be required. The Examiner must defer to the AMCD or Region if: • there is any question concerning the adequacy of therapy; • the applicant appears to be noncompliant with therapy; • the MWT demonstrates sleep deficiency; or • the applicant has developed some associated illness, such as right-sided heart failure.	No specific standards or guidelines	Sleep disorders that would result in gradual deterioration of performance of duties, sudden incapacitation, or would otherwise compromise shipboard safety, including required response in an emergency situation may be disqualifying.

* Source of information for FAA Regulations and Guidelines: http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/special_iss/all_classes/sleep_apnea/

† Source of information for Federal Railroad Administration Guidelines: http://www.fra.dot.gov/us/content/1586

‡ Source of information for Merchant Mariner Guidelines: http://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf

AMCD = Aerospace medical certification division; FAA = Federal aviation administration; MWT = Maintenance of wakefulness test.

Regulatory Medical Fitness Standards in Australia, Canada, the United Kingdom, New Zealand, and Sweden

Regulatory standards and guidance pertaining to sleep apnea and CMV driving in Australia, Canada, the United Kingdom, New Zealand, and Sweden are presented in Table 5.

Table 5. Regulations Pertaining to Sleep Apnea and CMV Driving from Selected Countries

Country	Regulation
Australia*	The criteria for an unconditional license are NOT met: • If the person has established SAS (sleep apnea on a diagnostic sleep study and EDS), with moderate to severe sleepiness, until treatment is effective. Consideration should be given to how long-distance drivers will comply with treatment such as CPAP. • If there is a history suggestive of sleep apnea in association with severe daytime sleepiness, until investigated and treated. Severe sleepiness is indicated by frequent self-reported sleepiness while driving, motor vehicle crashes caused by inattention or sleepiness or an ESS score of 16 to 24. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a specialist in sleep disorders, and the nature of the driving task, and subject to annual review: • For those with established SAS (sleep apnea on a diagnostic sleep study and ESS) who are on satisfactory treatment.
Canada†	The following recommendations should only be made by physicians familiar with the interpretation of sleep studies. • Regardless of apnea severity, all patients with OSA are subject to sleep schedule irregularities and subsequent sleepiness. Because impairment from sleep apnea, sleep restriction, and irregular sleep schedules may be interactive, all patients should be advised about the dangers of driving when drowsy. • Patients with mild OSA without daytime somnolence who report no difficulty with driving are at low risk for motor vehicle crashes and should be safe to drive any type of motor vehicle. • Patients with OSA, documented by a sleep study, who are compliant with CPAP or who have had successful UPPP treatment, should be safe to drive any type of motor vehicle. • Patients with moderate to severe OSA, documented by sleep study, who are *not* compliant with treatment and are considered at increased risk for motor vehicle crashes by the treating physician, should not drive any type of motor vehicle. • Patients with a high apnea-hypopnea index, especially if associated with right-heart failure or excessive daytime somnolence, should be considered at high risk for motor vehicle crashes. • Patients with OSA who are believed to be compliant with treatment but who are subsequently involved in a motor vehicle crash in which they were at fault should not drive for at least 1 month. During this period, their compliance with therapy must be reassessed. After the 1-month period, they may or may not drive depending on the results of the reassessment.
United Kingdom‡	Driving must cease until satisfactory control of symptoms has been attained, with ongoing compliance with treatment, confirmed by consultant /specialist opinion. Regular, normally annual licensing review required.

Country	Regulation
New Zealand**	Driving should cease for individuals who meet the high-risk driver profile as follows: • are suspected of having OSA syndrome where there is a high level of concern regarding the risk of excessive sleepiness while driving while the individual is waiting for the diagnosis to be confirmed by a sleep study • complain of severe daytime sleepiness and a history of sleep-related motor vehicle crashes or equivalent level of concern • have a sleep study that demonstrates severe OSA syndrome and either it is untreatable or the individual is unwilling or unable to accept treatment Individuals may resume driving or can drive if their OSA syndrome is adequately treated under specialist supervision with satisfactory control of symptoms. Consideration should be given to the type of driving and hours of driving an individual undertakes. If there is any residual risk of daytime sleepiness, medical practitioners should recommend a restriction in working hours or shift work. The Director of Land Transport Safety or the Director's delegate may impose license conditions for regular medical assessment. Medical follow-up may be delegated to the General Practitioner.
Sweden††	Possession (holding a driving license, tractor license, or taxi-driver license) • OSA syndrome constitutes grounds for denial of possession. This, however, does not apply in the case of successful treatment. • Regarding possession in Groups II and III, due consideration shall be given to the additional risks and dangers to traffic safety involved in such possession. Reappraisal (Reappraisal of possession through the requirement on a medical certificate or other medical statement) • A reappraisal shall occur at intervals considered suitable in each individual case.

* Source of information for Australia: http://www.austroads.com.au/aftd/index.html

† Source of information for Canada: http://www.cma.ca/index.cfm/ci_id/18223/la_id/1.htm

‡ Source of information for the United Kingdom: http://www.dvla.gov.uk/medical.aspx?keywords=medical

** Source of information for New Zealand: http://www.landtransport.govt.nz/licensing/docs/ltsa-medical-aspects.pdf

†† Source of information for Sweden: http://www.vv.se/filer/4796/9889eng000915.pdf

CPAP = Continuous positive airway pressure; EDS = Excessive day-time sleepiness; ESS = Epworth sleepiness scale; OSA = Obstructive sleep apnea; UPPP = Uvulopalatopharyngoplasty.

Methods

The *Methods* section provides a synopsis of how we identified and analyzed information for this report. The section briefly covers the key questions addressed, literature searches performed, the criteria used including studies, evaluation of study quality, assessment of the strength of the evidence base for each key question, and the methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, statistical approaches used, etc. are documented in appendices.

Key Questions

This evidence report addresses seven key questions. Each of these key questions was developed by FMCSA so that the answers to these questions would provide information that would be useful in updating their current medical examination guidelines. The seven key questions addressed in this evidence report are as follows:

Key Question 1: Are individuals with OSA at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Key Question 2: What disease-related factors are associated with an increased motor vehicle crash risk among individuals with OSA?

Key Question 3: Given the findings of Key Question 2, are individuals with OSA unaware of the presence of the factors that appear to be associated with an increased motor vehicle crash risk?

Key Question 4: Are there screening/diagnostic tests available that will enable examiners to identify those individuals with OSA who are at an increased risk for a motor vehicle crash?

Key Question 5: Which treatments have been shown to effectively reduce crash risk among individuals with OSA (as determined by crash rates or through indirect measures[7] of crash risk)?

Key Question 6: What is the length of time required following initiation of an effective treatment (determined by Key Question 5) for patients with OSA to reach a degree of improvement that would permit safe driving (as determined by crash rates or through indirect measures of crash risk)?

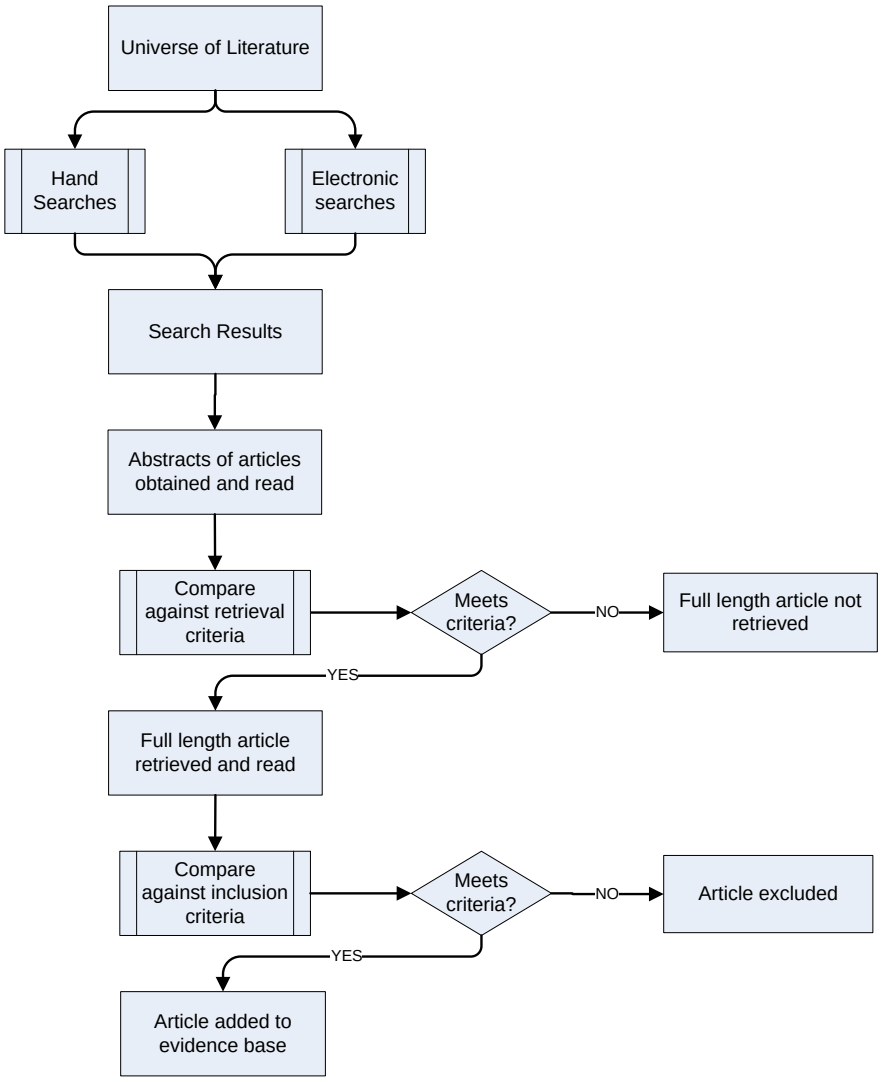
Key Question 7: How soon, following cessation of treatment (e.g., as a consequence of noncompliance), will individuals with OSA demonstrate reduced driver safety (as determined by crash rates or through indirect measures of crash risk)?

[7] Indirect measures of driver safety include the following: simulated driving, closed course driving, measures of cognitive function, measures of psychomotor function, and daytime sleepiness.

Identification of Evidence Bases

The individual evidence bases for each of the seven key questions addressed in this evidence report were identified using the multistage process captured by the algorithm presented in Figure 4. The first stage of this process consists of a comprehensive search of the literature. The second stage of the process consists of the examination of abstracts of identified studies in order to determine which articles will be retrieved. The final stage of the process consists of the selection of the actual articles that will be included in the evidence base.

Figure 4. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews that use a less rigorous approach to identifying and obtaining literature, thereby allowing a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias, because we obtain and include articles according to explicitly determined *a priori* criteria. Full details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 6.

Table 6. Electronic Databases Searched

Name of Database	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	2003 through April 30, 2007	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	2003 through 2007, Issue 2	http://www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	2003 through 2007, Issue 2	http://www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	2003 through 2007, Issue 2	http://www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	2003 through 2007, Issue 2	http://www.thecochranelibrary.com
ECRI Institute Library Catalog	2003 through 2007	ECRI Institute
EMBASE (Excerpta Medica)	2003 through April 30, 2007	OVID
Health Technology Assessment Database (HTA)	2003 through 2007, Issue 2	http://www.thecochranelibrary.com
MEDLINE	2003 through April 30, 2007	OVID
PsycINFO	2003 through April 30, 2007	OVID
PubMed (PreMEDLINE)	PreMEDLINE[sb] Searched March 30, 2007	http://www.pubmed.gov
TRIS Online (Transportation Research Information Service Database)	Searched April 30, 2007	http://ntlsearch.bts.gov/tris/index.do
U.K. National Health Service Economic Evaluation Database (NHS EED)	2003 through 2007, Issue 2	http://www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC™)	2003 through April 30, 2007	http://www.ngc.gov

Manual Searches

We reviewed journals and supplements maintained in ECRI Institute's collections of more than 1,000 periodicals. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant reports not identified by our electronic searches. In order to retrieve additional relevant information, we also performed hand searches of the "gray literature." Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. The latter documents do not appear in the peer-reviewed journal literature.

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions pertaining to whether a full-length article should be retrieved are usually based on a review of available abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with FMCSA. The retrieval criteria are presented in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If it was unclear whether a potentially relevant article met our retrieval criteria (e.g., no abstract was available for evaluation), the full-length version of that article was obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI Institute analyst who determined whether that article met a set of predetermined, question-specific, inclusion criteria. As was the case for the retrieval criteria, the inclusion criteria for this evidence report were determined *a priori* in conjunction with FMCSA. These inclusion and exclusion criteria are presented in Appendix C.

If on reading an article it was found not to meet the question-specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the reason(s) for its exclusion, are presented in Appendix D.

Evaluation of Quality and Strength of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focused on the overall *body* of the available evidence that was used to draw an evidence-based conclusion.(49) Using this approach, which is described briefly in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g., "Individuals with OSA are at increased risk for a motor vehicle crash") and a quantitative conclusion (e.g., "When compared to individuals who do not have OSA, the risk ratio for a motor vehicle crash among individuals with the disorder is 1.37; 95% CI: 1.03–1.74; P <0.005.").
As shown in Table 7, we assigned a separate strength-of-evidence rating to each of type of conclusion. Evidence underpinning a qualitative conclusion was rated according to its strength, and evidence underpinning quantitative conclusions was rated according to the stability of the effect-size estimate that was calculated.

Table 7. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature for moderate-strength conclusions.
Minimally acceptable	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions. ECRI Institute recommends frequent monitoring of the relevant literature.
Unacceptable	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI Institute recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect-Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect-size estimates that deemed to be stable are more unlikely to change significantly with the publication of new data than are unstable effect-size estimates.

Statistical Methods

The set of analytic techniques used in this report was extensive. In summary, random- and fixed-effects meta-analyses were used to pool appropriate data from different studies.(1-5,50-54) Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2.(6-8,50,55-57) Whenever appropriate, heterogeneity was explored using meta-regression techniques.(58-60) Sensitivity analyses were used to test the robustness of all findings.(9-11,61-64) The presence of publication bias was tested for using the "trim and fill" method.(65) All meta-analyses in this Evidence Report were performed using Comprehensive Meta-Analysis software.(12-14)

We calculated several different estimates of effect. The choice of effect-size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. Between-group differences in outcome measured using continuous data were analyzed in their original metric (if all included studies reported on the same outcome using the same metric) or the data were standardized into a common metric known as the standardized mean difference (SMD). Dichotomous data were analyzed using the rate ratio (RR) or the odds ratio (OR). Time-to-event data were analyzed using the hazard ratio (HR). The formulae for these effect-sizes and their variance are

presented in Table 8. If means and standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(66)

Table 8. Effect-Size Estimates Used in Evidence Report and their Variance

Effect-Size	Formula (Effect-Size)	Formula (Variance)
WMD	$\mu_{TG} - \mu_{CG}$	$\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2 + (n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)\left(\frac{1}{n_{TG}} + \frac{1}{n_{cg}}\right)$
SMD	$\frac{\mu_{TG} - \mu_{CG}}{\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2 + (n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}} + \frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} = mean (treatment group); μ_{CG} = mean (control group); s_{TG} = standard deviation (treatment group); s_{CG} = standard deviation (control group); n_{TG} = enrollees (treatment group); n_{CG} = enrollees (control group)		
Event Rate	$a/a+b$	$\ln\left[\frac{1}{a} + \frac{1}{a+b}\right]$
Where: a = number of individuals in cohort experiencing an event; b = number of individuals in cohort who did not experience an event		
RR (incidence)	$\frac{\left(\frac{a_{OSAs}}{pt_{OSA}}\right)}{\left(\frac{b_{control}}{pt_{control}}\right)}$	$\ln\left[\frac{1}{a_{OSA}} + \frac{1}{b_{control}}\right]$
Where: a = number of individuals with OSA who crashed; pt_{OSA} = rate denominator (OSA group); b = number of individuals without OSA who crashed; $pt_{control}$ = rate denominator (control group)		
OR	$\frac{\left(\frac{a}{b}\right)}{\left(\frac{c}{d}\right)} = \left(\frac{ad}{bc}\right)$	$\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$
RR	$\frac{\left(\frac{a}{a+c}\right)}{\left(\frac{b}{b+d}\right)}$	$\frac{1}{a} + \frac{1}{a+c} + \frac{1}{b} + \frac{1}{b+d}$
Where: a = number of individuals with OSA who crashed; b = number of individuals without OSA who crashed; c = number of individuals with OSA who did not crash; d = number of individuals without OSA who did not crash.		

Effect-Size	Formula (Effect-Size)	Formula (Variance)
HR	$\frac{O_{pi}/E_{pi}}{O_{ci}/E_{ci}}$	$\exp\left(\ln\left[\frac{1}{E_{pi}}+\frac{1}{E_{ci}}\right]\right)$
Where O_{pi} = observed number of events in treatment group; O_{ci} = observed number of events in control group; E_{pi} = log-rank expected number of events in treatment group; E_{ci} = log-rank expected number of events in control group		

HR = Hazard ratio; OR = Odds ratio; OSA = Obstructive sleep apnea; RR = Rate ratio; SMD = Standardized mean difference; WMD = Weighted mean difference.

Evidence Synthesis

This section summarizes the findings of our systematic review of the evidence pertaining to each of the key questions asked by FMCSA.

Key Question 1: Are individuals with OSA at an increased risk for a motor vehicle crash when compared to comparable individuals who do not have the disorder?

Identification of Evidence Base

To meet the aims of this section of the evidence report we searched for comparative trials that compared crash risk among individuals with OSA and otherwise comparable individuals who do not have the disorder. In addition, we looked for studies that compared the prevalence of OSA among cohorts of individuals who have or have not experienced a crash.

The evidence base identification pathway for Key Question 1 is summarized in Figure 5. Our searches[8] identified a total of 252 articles that appeared relevant to this key question. Following application of the retrieval criteria for this question, 64 full-length articles were retrieved and read in full. Seventeen of these 64 retrieved articles were found to meet the inclusion criteria[9] for Key Question 1 (Table 9). Table D-1 of Appendix D lists the 47 articles that were retrieved, read in full, and then excluded. The table also provides justification for their exclusion.

[8] See Appendix A for search strategies
[9] See Appendix C for inclusion criteria

Figure 5. Development of Evidence Base for Key Question 1

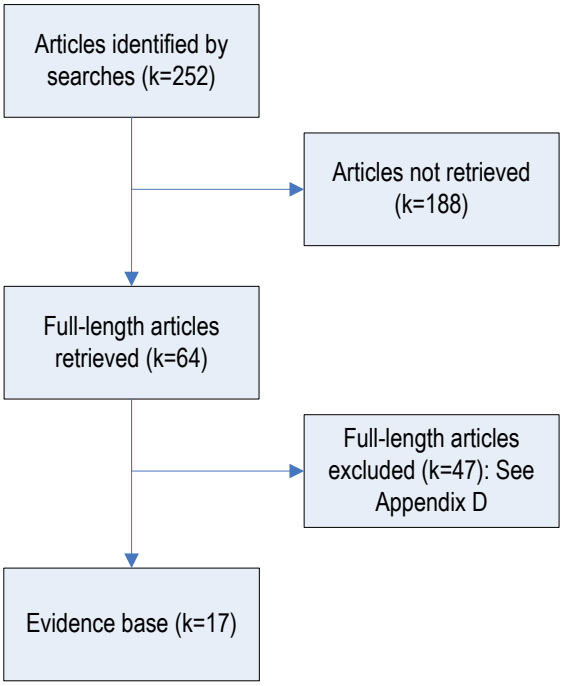


Table 9. Evidence Base for Key Question 1

Reference	Year	Study Location	Country
Commercial Motor Vehicle Drivers			
Howard et al.(48)	2004	Victoria	Australia
Stoohs et al.(67)	1994	California	USA
Noncommercial Motor Vehicle Drivers			
Barbe et al.(68)	2006	Barcelona	Spain
Kingshott et al.(69)	2004	Dunedin	New Zealand
Kumar et al.(70)	2003	New Delhi	India
Shiomi et al.(71)	2002	Aichi	Japan
Findley et al.(72)	2000	Colorado	USA
Horstmann et al.(73)	2000	Bern	Switzerland
Lloberes et al.(74)	2000	Barcelona	Spain
George and Smiley(75)	1999	Ontario	Canada
Teran-Santos et al.(76)	1999	Burgos and Santander	Spain
Young et al.(77)	1997	Wisconsin	USA
Cassel et al.(78)	1996	Marburg	Germany
Wu and Yan-Go(79)	1996	California	USA
Haraldsson et al.(80)	1990	Stockholm	Sweden
Aldrich M.S.(81)	1989	Michigan	USA
Findley et al.(82)	1988	Virginia	USA

Evidence Base

This subsection provides a brief description of the key attributes of the 17 studies that comprise the evidence base for Key Question 1. Here we discuss applicable information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 10.

Table 10. Key Study Design Characteristics of Studies that Address Key Question 1

Reference	Year	Study Design	Comparison	Diagnosis of Sleep Apnea	Factors controlled for (if compared to nonapneic controls)?	Driving exposure controlled for?	Primary Outcome	Definition of Crash	Outcome self-reported?
Commercial Motor Vehicle Drivers									
Howard et al.(48)	2004	Case-Control Study†	2,342 commercial drivers completed questionnaire study	Symptom diagnosis (MAP ≥0.5 and ESS score 11 – 24)	Not Reported	Yes, hours of driving	Difference in crash rate	Any single- or multiple-motor vehicle crash where enrollee was driver	Yes (questionnaire)
Stoohs et al.(67)	1994	Case-Control Study†	46 commercial drivers with sleep-disordered breathing (SDB) compared with 44 commercial drivers without SDB.	Oxygen desaturation index (ODI) ≥10	Not Reported	Yes	Difference in crash rate	A motor vehicle crash was defined as the collision of the index case's vehicle with a stationary or moving object or as driving off the road in the absence of an obstacle.	Yes (questionnaire) No (employer records)
Noncommercial Motor Vehicle Drivers									
Barbe et al.(68)	2006	Case-Control Study†	76 individuals with OSA syndrome (OSAS) compared with 73 individuals without OSAS.	AHI >20	Gender, age	Yes	Difference in crash rate	A motor vehicle crash was defined as a crash resulting in property damage >USD 500 and/or personal injury	No (insurance company records)
Kingshott et al.(69)	2004	Case-control study*	60 individuals who had been in a police-reported traffic crash compared with 60 individuals no-crash.	AHI and ESS	Gender, age, BMI	Yes	Difference in proportion of individuals with OSA	Driver in a single-vehicle crash or causative driver in a multiple-vehicle crash	Yes (questionnaire)
Kumar et al.(70)	2003	Case-Control Study†	20 individuals with OSAS compared with 40 individuals without OSAS.	Sleep Questionnaire	Gender, age	No	Difference in crash rate	Any motor vehicle crash where enrollee was driver	Yes (questionnaire)
Shiomi et al.(71)	2002	Case-Control Study†	448 individuals with OSA-hypopnea syndrome (OSAHS) compared with 106 simple snorers.	AHI and ESS	Not Reported	No	Difference in crash rate	Any motor vehicle crash where enrollee was driver	Yes (questionnaire)

Reference	Year	Study Design	Comparison	Diagnosis of Sleep Apnea	Factors controlled for (if compared to nonapneic controls)?	Driving exposure controlled for?	Primary Outcome	Definition of Crash	Outcome self-reported?
Findley et al.(72)	2000	Case-Control Study†	50 individuals with OSA compared with all drivers in Colorado.	Occurrence of ≥5 apneas plus hypopneas per hour of sleep	Gender, age	No	Difference in crash rate	A motor vehicle crash was defined as a crash resulting in property damage >$500 and/or personal injury for which the driver was convicted of a traffic violation. These crashes were considered to be those in which the driver was at fault.	No (State Records)
Horstmann et al.(73)	2000	Case-Control Study†	156 individuals with SAS compared with 160 individuals without SAS. These two groups were compared with all drivers in Switzerland.	AHI ≥10/hour	Gender, age	Yes	Difference in crash rate	All reported crashes were subdivided into those with property damage <$600 and into those with property damage >$600 or personal injury.	Yes (questionnaire)
Lloberes et al.(74)	2000	Case-Control Study†	122 individuals with OSAS compared with 67 nonapneic snorers, and 40 individuals without OSAS.	AHI ≥10/hour	Age	No	Difference in crash rate	Any motor vehicle crash or incidence of driving off the road where enrollee was driver	Yes (questionnaire)
George and Smiley(75)	1999	Case-Control Study†	460 individuals with OSA compared with 581 individuals without OSA. These two groups were compared with all drivers in Ontario.	AHI ≥10/hour	Gender, age	No	Difference in crash rate	Any motor vehicle crash where enrollee was driver	No (State Records)
Teran-Santos et al.(76)	1999	Case-control study*	102 individuals who received emergency treatment after highway traffic crashes compared with 152 individuals no-crash.	AHI ≥5/hour	Gender, age	Yes	Difference in proportion of individuals with sleep apnea	Any motor vehicle crash where enrollee was driver	Yes (questionnaire)

Reference	Year	Study Design	Comparison	Diagnosis of Sleep Apnea	Factors controlled for (if compared to nonapneic controls)?	Driving exposure controlled for?	Primary Outcome	Definition of Crash	Outcome self-reported?
Young et al.(77)	1997	Case-Control Study†	221 individuals with SDB compared with 692 individuals without SDB.	AHI ≥5/hour	Not Reported	Yes	Difference in crash rate	A motor vehicle crash was defined as a crash resulting in property damage ≥$500 and/or personal injury, or if police or other law enforcement personnel were at the crash scene and filed a report.	No (State Records)
Cassel et al.(78)	1996	Case-Control Study†	59 individuals with SDB compared with all drivers in Germany.	AHI	Not Reported	Yes	Difference in crash rate	Any motor vehicle crash where enrollee was driver	Yes (questionnaire)
Wu and Yan-Go(79)	1996	Case-Control Study†	173 individuals with SAS compared with 80 individuals without SAS.	RDI or AHI >5/hour	Not Reported	No	Difference in crash rate	Any motor vehicle crash or near-miss where enrollee was driver	Yes (questionnaire)
Haraldsson et al.(80)	1990	Case-Control Study†	140 individuals with SAS-associated symptoms compared with 142 individuals without SAS-associated symptoms.	Clinical triad of sleep apnea: snoring, sleep disturbance, daytime sleepiness	Not Reported	Yes	Difference in crash rate	Crashes were categorized as single-car (driving off the road) or combined-car (two or more vehicles) crashes.	Yes (questionnaire)
Aldrich M.S.(81)	1989	Case-Control Study†	228 individuals with sleep apnea compared with 70 individuals without sleep apnea.	RDI	Gender, age	No	Difference in crash rate	Any motor vehicle crash or near-miss where enrollee was driver	Yes (questionnaire)
Findley et al.(82)	1988	Case-Control Study†	29 individuals with OSA compared with 35 individuals without OSA. These two groups were compared with all drivers in Virginia.	AHI >5/hour	Not Reported	Yes	Difference in crash rate	A motor vehicle crash was defined as a crash resulting in property damage >$500 and/or personal injury. A driver was at fault if he was convicted of a traffic violation that contributed to the crash.	No (State Records)

*A case-control study in which cases are defined according to whether individuals have experienced a crash and controls consist of a cohort of individuals who have not.

†A case-control study in which cases are defined according to the presence of OSA and controls consist of a cohort of individuals who do not.

AHI = Apnea-hypopnea index; BMI = Body mass index; ESS = Epworth Sleepiness Score; MAP = Multivariate apnea prediction; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnea; OSAHS = Obstructive sleep apnea-hypopnea syndrome; OSAS = Obstructive sleep apnea syndrome; RDI = Respiratory disturbance index; SAS = Sleep apnea syndrome; SDB = Sleep-disordered breathing; USD = United sleep diagnostics.

The 17 included studies used 1 of 2 different case-control methodologies. The most commonly used methodology (*k = 15*) was to select drivers with OSA (cases) and compare the incidence of crash over a defined time period with the incidence of crash occurring over a similar time period among comparable individuals without the condition. The less commonly used approach (*k = 2*) was to select cohorts on the basis of crash involvement and compare the prevalence of OSA among individuals who experienced a crash (cases) and those who did not (controls).

A design problem common to many risk-assessment studies is the failure to control adequately for exposure. In this instance, the exposure variables of critical importance are the number of miles driven per unit time and the time frame over which data were collected. If cases and controls are not well matched for exposure to risk, then any observed differences in the risk may simply be the consequence of differences in exposure. A majority of the included studies attempted to control for both of these exposure variables.

Crash rates were determined from data obtained from two primary sources: databases and questionnaires. In order for data from databases to be informative, the relevant information contained within it must be precise. Since we have no way of determining the precision of the information contained within any of the databases used to inform the studies included in this report, the degree of confidence that one may have in data extracted from these databases is not clear. The degree of confidence that one can have in crash rates derived from questionnaires is also unclear, primarily because questionnaires depend on reliable reporting by the individual being questioned.

Quality of Evidence Base

The findings of our assessment of the quality of the studies that comprise the evidence base for Key Question 1 are summarized in Table 11. Complete details of our quality assessment can be found in the Study Summary Tables presented in Appendix G. Our assessment found that the quality of the included studies was not high. Four of the 17 included studies were graded as being moderate quality. The remaining 11 studies were graded as low quality.

Table 11. Quality of the Studies that Assess Key Question 1

Reference	Year	Quality Scale Used	Quality
Howard et al.(48)	2004	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Stoohs et al.(67)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Barbe et al.(68)	2006	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Kingshott et al.(69)	2004	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Kumar et al.(70)	2003	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Shiomi et al.(71)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Findley et al.(72)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Horstmann et al.(73)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Lloberes et al.(74)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
George and Smiley(75)	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Teran-Santos et al.(76)	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Young et al.(77)	1997	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Cassel et al.(78)	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Wu and Yan-Go(79)	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Haraldsson et al.(80)	1990	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Aldrich M.S.(81)	1989	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Findley et al.(82)	1988	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate

Generalizability of Evidence to Target Population

Important characteristics of the individuals represented in the 17 studies that comprise the evidence base for Key Question 1 are presented in Table 12. The information presented in this table demonstrates that currently available data that is directly generalizable to CMV drivers is extremely limited. Only two included studies enrolled distinct populations of CMV drivers.(48,67) The remainder of the studies included private motor vehicle license holders, an unknown number of whom may have held commercial driver licenses. The generalizability of the findings of these latter studies to CMV drivers is unclear.

Table 12. Individuals with OSA Enrolled in Studies that Address Key Question 1

Reference	Year	Number of Individuals with OSA included (n =)	Diagnosis (e.g., PSG, questionnaire)	Severity of OSA and How was Assessed (n =)	Sleepiness and How was Assessed (n =)	Age Distribution	% Male	% CMV Drivers	Driving Exposure	Ethnicity	Generalizability to Target Population
Commercial Motor Vehicle Drivers											
Howard et al.(48)	2004	161	PSG, ESS, and MAP questionnaire	**RDI** 5.0 - 14.9 34.8% (27.5 - 42.7)* 15.0 - 29.9 14.3% (9.3 - 20.7)* ≥30.0 10.6% (6.3 - 16.4)* **SAS** (RDI ≥5, ESS ≥11) 15.8% (10.5 - 22.5)*	**ESS** 7.69 ±4.34 >11: 24.1% (17.6 - 31.5)*	48 ±9	99	100	Minimum 10 hours/week for work	NR	Good
Stoohs et al.(67)	1994	90	Questionnaire and Ambulatory screening device: the Mesam IV®	**ODI** <10 n = 44 ≥10 <20 n = 26 ≥20 <30 n = 10 >30 n = 10	NR	36 ±9	93	100	NR	NR	Good
Noncommercial Motor Vehicle Drivers											
Barbe et al.(68)	2006	76	PSG	Severity ranged from AHI = 21 to AHI = 122 AHI mean = 60 (SD = 2)	**ESS** Cases: 12 ±1† Control: 3 ±2†	Cases: 49 ±1† Controls: 46 ±1†	NR	NR	km driven, 1,000 km/year Cases: 25 ±2† Controls: 21 ±2†	NR	Unclear
Kingshott et al.(69)	2004	60	PSG	**AHI** Mean (SD) = 8 (9) AHI >5 48% AHI >15 15% AHI >5 + ESS ≥10 20% AHI >15 + ESS ≥10 7%	**ESS** Cases: 8 ±4 Controls: 8 ±4 **MWT** Cases: 17 ±4 minutes Controls: 18 ±3 minutes	Cases: 49 ±11 Controls: 49 ±11	Cases: 48 Controls: 48	NR	km driven/year Cases: 15,410 ±12,301 Controls: 15,253 ±21,007	Caucasian Cases: 88% Controls: 90%	Unclear
Kumar et al.(70)	2003	20	Questionnaire	NR	**ESS** Cases: 13.6 6.1 Controls: 4.2 ±4.1	Cases: 41 ±6 Controls: 41 ±8	Cases: 100 Controls: 100	NR	NR	NR	Unclear

Reference	Year	Number of Individuals with OSA included (n =)	Diagnosis (e.g., PSG, questionnaire)	Severity of OSA and How was Assessed (n =)	Sleepiness and How was Assessed (n =)	Age Distribution	% Male	% CMV Drivers	Driving Exposure	Ethnicity	Generalizability to Target Population
Shiomi et al.(71)	2002	448	PSG	**AHI** 5 - 15 n = 155 15 - 30 n = 111 >30 n = 182	**ESS** >11 n = 93	49 ±14	89	NR	NR	NR	Unclear
Findley et al.(72)	2000	50	PSG	**AHI** 37 (3.8) †	NR	56 (2) †	86	NR	NR	NR	Unclear
Horstmann et al.(73)	2000	156	PSG	**AHI** 10 - 34 n = 78 >35 n = 78 median = 20	**ESS** Cases: 12.9 ±5 .5 Controls: 7.2 ±4.7	Cases: 56 ±10 Controls: 56 ±12	Cases: 92 Controls: 90	NR	Cases # of drivers (%):130 (83) Mean = 19,416 km /driver /year Median = 15,000 km /driven /year Controls # of drivers (%):140(87) Mean = 14,160 km /driver /year Median = 10,000 km /driven /year	NR	Unclear
Lloberes et al.(74)	2000	122	PSG	**AHI** mean = 42.5 (SD = 2)	NR	Cases: 51 ±9 Controls: 50 ±9	Cases: 95 Controls: 84	NR	NR	NR	Unclear
George and Smiley(75)	1999	460	PSG	**AHI** 10 - 25 n = 182 26 - 40 n = 85 >40 n = 193	NR	Cases: 51 ±12 Controls: 52 ±12	Cases: 88 Controls: 90	NR	NR	NR	Unclear
Teran-Santos et al.(76)	1999	102	PSG and nocturnal respiratory polygraphy (at home)	**AHI** ≥5 n = 29 ≥10 n = 21 ≥15 n = 17	**ESS** Cases: 5.9 Controls: 5.7	Cases: 44 ±9 Controls: 43 ±9	77	NR	Cases 24,011 ±22,359 Km driven/year 20 ±10 years of driving Controls 16,978 ±18,760 km driven/year 19 ±8 years of driving	NR	Unclear
Young et al.(77)	1997	221	PSG	**AHI** 5 - 15 n = 133 >15 n = 88	ESS MSLT	45 ±8 (range, 30 - 60)	59	NR	NR	NR	Unclear

Reference	Year	Number of Individuals with OSA included (n =)	Diagnosis (e.g., PSG, questionnaire)	Severity of OSA and How was Assessed (n =)	Sleepiness and How was Assessed (n =)	Age Distribution	% Male	% CMV Drivers	Driving Exposure	Ethnicity	Generalizability to Target Population
Cassel et al.(78)	1996	59	PSG	AHI	Questionnaire MSLT	49 ±1†	100	NR	29,860 ±2,886 km driven/year†	NR	Unclear
Wu and Yan-Go(79)	1996	173	PSG	AHI >5 RDI >5	NR	SAS 17 - 24: 3% 25 - 44: 31% 45 - 64: 49% >64: 18% Non-SAS 17 - 24: 9% 25 - 44: 36% 45 - 64: 43% >64:13%	SAS 79 Non-SAS 53	NR	NR	NR	Unclear
Haraldsson et al.(80)	1990	140	Questionnaire	SAS Incomplete n = 67 No sleep spell n = 35 Sleep spell n = 38 Complete n = 73	NR	Cases: 48 ±9 (range: 30 - 69) Controls: 46 ±11 (range: 30 - 69)	Cases: 100 Controls: 100	NR	Cases 24 ±2 10^3 km 1,800 10^3 km (accumulated) Controls 20 ±3 10^3 km 2,900 10^3 km (accumulated)	NR	Unclear
Aldrich M.S.(81)	1989	181	PSG	RDI	MSLT	Cases: 50 Controls: 43	NR	NR	NR	NR	Unclear
Findley et al.(82)	1988	29	PSG	Desaturation per hour of sleep (at least 4%)	NR	Cases: 47 ±12 Controls: 45 ±12	NR	NR	Case 13,150 ±7,350 miles driven/year Control 11,290 ±7,780 miles driven/year	NR	Unclear

Unless otherwise stated, data are expressed as mean ±SD

AHI = Apnea-hypopnea index; CMV = Commercial motor vehicle; ESS = Epworth sleepiness scale; MAP = Multivariable apnea prediction; MSLT = Multiple sleep latency tests; MWT = Maintenance of wakefulness test; NR = Not reported; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnea; PSG = Polysomnography; RDI = Respiratory disturbance index;SAS = Sleep apnea syndrome; SD = Standard deviation.

*Data expressed as proportion (95%CI)

† Data expressed as means ±SEM

Findings

As stated previously, the evidence base for Key Question 1 is comprised of two distinct types of case-control studies. Fifteen studies compared crash risk among individuals with OSA (cases) with a comparable group of individuals who did not have the disorder (controls). Two studies compared the prevalence of OSA among individuals who had been involved in a crash (cases) with a comparable group of individuals who had not (controls). Although both types of studies may be considered to address the same question from a qualitative perspective ("Does OSA represent an increased crash risk?"), they differ significantly from a quantitative perspective. Outcome data from the former set of studies were presented as an RR[10]. Outcome data from the latter group of studies were presented as the OR[11].

Studies of OSA and Crash Risk among CMV Drivers

Two included studies presented data directly relevant to the question of whether OSA has an impact on CMV driver safety.(48,67) Both of these studies were designed specifically to examine the effects of SDB on crash risk among CMV drivers. Because of the direct relevance of data from these studies to CMV drivers, we discuss the findings of these studies separately from the remainder of the studies that comprise the evidence base for Key Question 1.

Study of Howard and Colleagues

Howard et al.(48) (Quality Rating: Low) compared crash risk among drivers with SAS (symptom diagnosis) and drivers not diagnosed with SAS (controls). They measured the prevalence of excessive sleepiness and SDB, and assessed crash-risk factors in 2,342 respondents to a questionnaire distributed to a random sample of 3,268 Australian commercial vehicle drivers and another 161 drivers among 244 invited to undergo PSG. Howard et al. presented the OR for having a crash in the past three years in drivers with SAS adjusted for age, hours of driving, and alcohol intake. Drivers diagnosed with SAS (Multivariable Apnea Prediction Score ≥0.5 [MAPS] and ESS score ≥11) were found to be at an increased risk for motor vehicle crash (OR = 1.3, 95% 1.00-1.69). The value of the findings of this study is weakened by the fact that individuals were diagnosed with sleep apnea using questionnaires only. The accuracy of this diagnosis was not confirmed via sleep lab investigations. Because the sensitivity and specificity of the instruments used in the diagnosis are not 100%,(83-87) it is unclear whether all individuals had received a correct diagnosis.

Study of Stoohs and Colleagues

Stoohs et al.(67) (Quality Score: Moderate) assessed a possible independent effect of sleep-related breathing disorders on traffic crashes in long-haul commercial truck drivers. The study design included integrated analysis of recordings of sleep-related breathing disorders, and self-reported and company-recorded automotive crashes. A cross-sectional population of 90 commercial long-haul truck drivers 20 to 64 years of age was studied. Main outcome measures included presence or absence, as well as severity, of sleep-disordered breathing and frequency of automotive crashes.

---

[10] The incidence of crash among individuals with OSA divided by the incidence of crash among comparable individuals who do not have OSA.

[11] The odds of an individual who crashed having OSA divided by the odds of an individual who did not crash having OSA.

The study was performed at the main hub of a long-haul trucking company. All company truck drivers who came through this loading point during a 3-week period were asked to participate in the study. The following information was collected:

- Every volunteer was asked to complete a questionnaire on sleeping habits and snoring and to report the number of driving crashes in which they had been involved over the last five years.
- The questionnaire consisted of 20 questions on patient demographics and daytime functioning, daytime sleep tendency, alertness, snoring, smoking history, and sleep quality. Questions were answered on a 5-point scale, in which 1 = never and 5 = always.
- Crash information for each driver over the last five years was obtained from company crash records. Drivers' self-reports of work-related truck crashes and crashes in private automobiles for the same time period were also obtained. A "crash" was defined as the collision of the index case's vehicle with a stationary or moving object or as driving off the road in the absence of an obstacle.
- Any volunteer who was planning to spend the night at the main hub before leaving with the next payload was asked to undergo nocturnal monitoring, either in a company trailer on the premises or in his/her own designated trailer kept in the company lot.

Two hundred thirteen drivers were scheduled to spend the night at the facilities. Of these, 193 (92%) agreed to undergo monitoring during sleep: 34 had to terminate the monitoring prematurely due to the availability of a truck load, and their data had to be discarded. Subjects who agreed to be monitored were tested overnight with an ambulatory screening device, the Mesam IV®. The device is a microprocessor that continuously monitors four variables throughout the night: heart rate, snoring sounds, SaO_2 (SaO_2), and body position/movement. Each individual received a sleep log in which to record lights-out and lights-on times, as well as behavioral awakenings and time spent awake. At morning awakening, subjects were asked to fill out a questionnaire rating sleep quality, sleep disturbances, and disturbances related to the equipment.

Stoohs et al. performed 159 recordings of appropriate duration for analysis. Because a portion of the monitored sample included student drivers with little professional driving experience, the authors decided only to include drivers with a driving history ≥2 months. Overnight recordings, completed questionnaires, and crash records were analyzed for 90 truck drivers.

Analyses of overnight recordings using the Mesam IV were used to identify obstructive hypopnea and apnea. The sleep logs were used to calculate total sleep time (TST) and the ODI. The ODI was calculated by dividing the total number of SaO_2 drops >3% by the determined TST in hours. One-way analysis of variance was performed to determine significance of changes between groups. Student's *t* test was applied for testing means of two groups. Pearson product moment correlations were used to determine the interdependence between sets of variables.

For analysis, Stoohs et al. considered the total number of vehicle crashes. They obtained information on mileage both from the trucking company and from the drivers' self-reported usage of private vehicles. All crash rates were adjusted for annual mileage of individual truck drivers. The findings of this study are summarized in Table 13.

Table 13. Findings of Stoohs et al.

Explanatory Variable	Findings	Significant (P <0.05)?
Total number of crashes	42 crashes 4 drivers = 2 crashes 2 drivers = 3 crashes	NA
Crashes and sleep-disordered breathing (SDB)	Drivers diagnosed with SDB (ODI ≥10) accounted for 23 of the 42 crashes, whereas drivers without SDB (ODI <10) caused 19 of all reported crashes.	No
	Drivers with SDB caused twice as many crashes/miles driven (0.085 crashes/10,000 miles) than drivers without SDB (0.046 crashes/10,000 miles).	No
Crashes and severity of SDB	Though crash frequency was about 100% higher in drivers with SDB, increasing severity of SDB was not significantly associated with an increase in crash frequency.	No
Crashes and excessive daytime sleepiness (EDS)	There was significantly higher crash frequency in drivers complaining of EDS (0.18 crashes/10,000 miles) as opposed to drivers without a complaint of EDS (0.06 crashes/10,000 miles).	Yes
	Using the scores for self-reported sleepiness, the isolated use of EDS as a predictive parameter for the occurrence of crashes had a sensitivity of 9% and a specificity of 92%.	NA
Crashes and obesity	Nonobese drivers (BMI <30 kg/m^2) had a mean of 0.045 crashes/10,000 miles compared to a mean of 0.1 crashes/10,000 miles in obese truck drivers.	Yes
	Nonobese truck drivers without SDB caused 77% more crashes/10,000 miles than nonobese drivers with nocturnal breathing abnormalities.	No
	Obese truck drivers with SDB caused 45% more crashes/mile driven than obese drivers without SDB.	No
	Using the scores for obesity (≥30 kg/m^2) as a predictor for driving crashes, this predictor had a sensitivity of 49% and a specificity of 71%.	NA
Crashes, EDS, and obesity	When combined, EDS and a BMI ≥30 kg/m^2 had a sensitivity of 53% and a specificity of 68% in predicting drivers with crashes.	NA
Crashes, SDB, EDS, and obesity	When combined, SDB, EDS and a BMI ≥30 kg/m^2 had a sensitivity of 76% and a specificity of 35% in predicting drivers with crashes.	NA

BMI = Body mass index; EDS = Excessive daytime sleepiness; ODI = Oxygen desaturation index; NA = Not applicable; SDB = Sleep disordered breathing.

Studies of Effect of OSA on Crash Risk in General Driver Population

Seventeen included studies provided data pertaining to the influence of OSA on the safety of the general driver population.[12] As noted above, crash risk was assessed using two different approaches. The first approach compared the prevalence of OSA among a group of individuals who had experienced a motor vehicle crash with that observed among a group of individuals who had not experienced such a crash. The measure of the difference in crash risk measured by this type of study is usually the OR (the odds of having OSA having experienced a motor vehicle crash divided by the odds of having OSA having not experienced a crash). For ease of communication, we henceforth refer to these studies as "OR studies."

The second approach to determining the risk associated with OSA and driver safety is to compare the incidence rate of motor vehicle crashes that occur among individuals who have OSA with the crash rate among comparable individuals who do not have the disorder. The measure of the difference in crash risk reported by this type of study is usually the RR (the ratio of crash incidence observed among individuals with OSA and comparable individuals who do not have the disorder). Henceforth, we refer to these studies as "RR studies."

[12] 15 studies plus the studies of Howard et al.(48) and Stoohs et al.(67)

OSA and Crash Risk: Findings of Crash RR Studies

Fifteen included studies reported on the incidence of crashes occurring among populations of individuals with OSA and the incidence of crashes occurring among individuals without the disorder.(48,67,68,70-75,77-82) The findings of these studies are presented in Table 14.

Table 14. Crash Risk in Drivers with OSA compared to Drivers without OSA

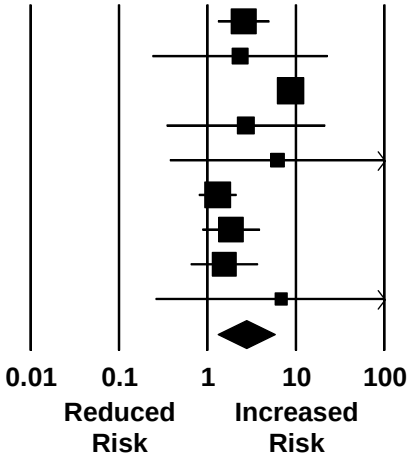
Reference	Year	Units	Crash Rate Data					Evidence of Increased Crash Risk
			Cases	Controls	Rate Ratio (95% CI)	Adjusted for…	*P* =	
Commercial Motor Vehicle Drivers								
Howard et al.(48)	2004	Odds Ratio of having a crash in past 3 years	1.30 (1.00 – 1.69)		NC	Age, hours of driving, alcohol intake	0.05	Yes
Stoohs et al.(67)	1994	Crashes per 10,000 miles per driver per year	0.086	0.046	1.85 (0.87-3.95)*	Miles driven	0.113*	No
Noncommercial Motor Vehicle Drivers								
Barbe et al.(68)	2006	Crashes per 1,000,000 km per driver over 2-year period	9.20	3.63	2.57 (1.30–5.05)	km driven	0.006*	Yes
Kumar et al.(70)	2003	Number of individuals who crashed	4	0	NC†		<0.001	Yes
Shiomi et al.(71)	2002	Crashes per driver per year	0.018*	0.008*	2.34 (0.24-23.16)*		0.467*	No
Findley et al.(72)	2000	Crashes per driver per year	0.07	0.0113*	6.20 (0.37-102.90)*	Age, gender	0.203	No
Horstmann et al.(73)	2000	Crashes per 1,000,000 km per driver per year	2.27*	0.26*	8.72 (6.18-12.30)*	km driven	<0.001*	Yes
Lloberes et al.(74)	2000	Crashes per driver per year	0.068*	0.025*	2.72 (0.34-21.66)*		0.345*	No
George and Smiley(75)	1999	Crashes per driver per year	0.067*	0.052*	1.31 (0.79-2.16)*		0.297*	No
Young et al.(77)	1997	Odds Ratio of having a crash in past 5 years	Habitual snorer, AHI <5: 1.5 (1.0-2.4) AHI 5-15: 1.9 (0.9-3.8) AHI >15: 1.6 (0.8-3.1)		NC	Age, miles driven per year, gender	NS	No
Cassel et al.(78)	1996	Crashes per 100,000 km over 5-year period	0.8	0.42	1.9 (NC‡)	km driven	NC	Yes
Wu and Yan-Go(79)	1996	Odds Ratio of having a crash	2.58 (1.06 – 6.31)		NC†	Alcohol intake, coffee intake, passing destination, falling asleep, history of D.P.S.L.††	0.037	Yes
Haraldsson et al.(80)	1990	Crashes per driver per year assuming each driver drives 24,000 km/year	0.121*	0.078*	1.55 (0.64-3.76)*	km driven	0.330*	No
Aldrich M.S.(81)	1989	Crashes per driver	1.94*	1.85*	1.05 (NC†)		NS	No
Findley et al.(82)	1988	Crashes per driver per year	0.082*	0.012*	6.83 (0.26-181.69)*		0.251*	No

*Calculated by ECRI Institute; estimates of confidence intervals based on transformation of available data to crashes/person-year. Effect-Size estimates >1.0 indicate that apneics are at increased risk for a motor vehicle crash than comparison group; †No time period reported for crash data; ‡Number of German drivers not reported; ††D = severe dizziness episodes, P = Parkinson's disease, S = seizures/epilepsy, L = loss of consciousness; AHI = Apnea-hypopnea index; NC = Not Calculated.

Nine included studies (Quality Rating: Low) provided enough data to determine the crash RR and 95% confidence intervals between individuals who have OSA and comparable individuals without the disorder.(67,68,71-75,80,82) A test of homogeneity found that the findings of the nine studies were heterogeneous (Q = 48.87, *P* <0.001; I^2 = 83.63). Because the evidence base consisted of less than 10 studies, we did not attempt to explore this heterogeneity using meta-regression techniques[13]. Rather we pooled these data using a random-effects meta-analysis (Figure 6).

Figure 6. Crash Risk among Individuals with OSA Compared to Controls (Random-effects Meta-analysis)

Study name	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Barbe	2.570	1.304	5.065	2.727	0.006
Shiomi	2.342	0.237	23.159	0.728	0.467
Horstmann	8.719	6.179	12.303	12.326	0.000
Lloberes	2.720	0.342	21.658	0.945	0.345
Findley 2000	6.195	0.373	102.902	1.272	0.203
George	1.306	0.791	2.158	1.043	0.297
Stoohs	1.848	0.865	3.947	1.586	0.113
Haraldsson	1.551	0.641	3.756	0.973	0.330
Findley 1988	6.833	0.257	181.694	1.148	0.251
	2.722	**1.295**	**5.722**	**2.642**	**0.008**



The findings of this meta-analysis provides support for the contention that individuals with OSA are at a significantly increased risk for experiencing a motor vehicle crash when compared to comparable individuals without OSA (Crash RR = 2.72, 95% CI: 1.30-5.72: p = 0.008). In other words, if one assumes that the underlying crash risk for a CMV driver is 0.08 crashes per person-year, the crash risk for a CMV driver with OSA can be estimated to be 0.21 (95% CI: 0.10 to 0.46) crashes per person-year.

A series of sensitivity analyses (Appendix H) demonstrated our finding that individuals with OSA are at an increased risk for a motor vehicle crash to be robust. While the quality of the studies was not high, the data were qualitatively consistent, and the magnitude of the difference in crash risk is very large. Consequently, one can be reasonably confident that future research findings are unlikely to overturn our findings.

[13] ECRI requires at least 10 studies for meta-regression or subgroup analysis to be attempted.

Findings of Studies that compared the Prevalence of OSA among Drivers who Did and Did Not Crash

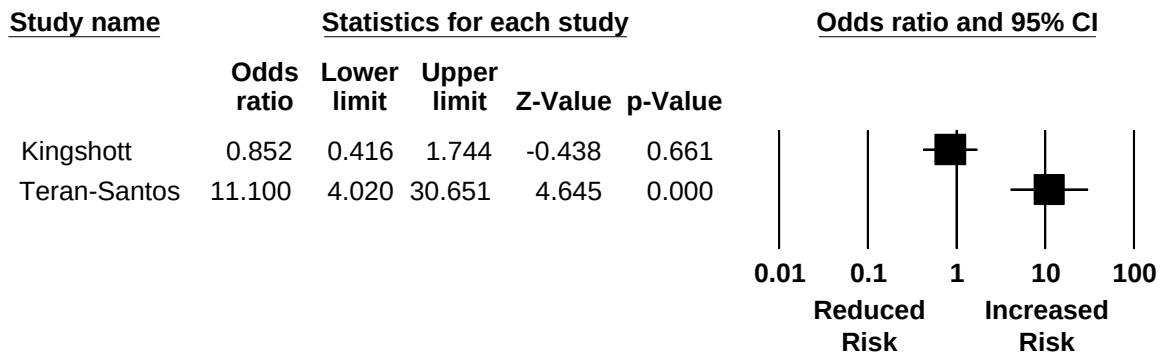
Two of the 17 studies (Quality Rating: Moderate) presented data on the odds of an individual who experienced a crash having OSA relative to the odds of a comparable individual who did not crash having OSA.(69,76) The findings of these studies are summarized in Table 15 and are represented graphically in Figure 7 below.

Table 15. Findings of OR Studies

Reference	Year	Units	Crash Rate Data				
			% with OSA (crashers)	% with OSA (noncrashers)	Effect Size (95% CI)	*P* =*	Evidence of Increased Crash Risk
Kingshott et al.(69)	2004	% having OSA	48 (AHI >5)	52 (AHI >5)	OR = 0.85* (0.42–1.74)	0.661	No
Teran-Santos et al.(76)	1999	% having OSA	28.4 (AHI ≥5)	4.6 (AHI ≥5)	OR = 11.4† (4.0–30.5)	<0.001	Yes

AHI = Apnea-hypopnea index; OR = Odds ratio; OSA = Obstructive sleep apnea. *Calculated by ECRI Institute from reported data; †adjusted for alcohol consumption, visual-refraction disorders, BMI, years of driving, age, involvement in previous crashes, use of medication causing drowsiness, smoking, work and sleep schedule, km driven per year, and coexisting conditions (including psychiatric disorders and arterial hypertension)

Figure 7. OSA and Crash Risk (OR)



The forest plot suggests that the data from the two included studies are inconsistent. One of the two studies suggested that OSA increased crash risk,(69) and one study found no evidence of an increase or a decrease in crash risk.(69)

Summary of Findings

A number of conclusions can be drawn from the findings of the analyses described above. These conclusions are presented below:

Drivers of CMVs

- **CMV drivers with OSA are at an increased risk for a crash when compared to their counterparts who do not have the disorder (Strength of Evidence: Acceptable).**
  - **A precise estimate of the magnitude of this increased risk cannot be determined at this time.**

Two studies presented data directly relevant to the question of whether OSA has an impact on CMV driver safety.(48,67) Howard et al.(48) (Quality Rating: Low) compared crash risk among drivers with

SAS (symptom diagnosis) and drivers not diagnosed with SAS (controls). Drivers diagnosed with SAS (MAPS ≥0.5 and ESS score ≥11) were found to be at an increased risk for motor vehicle crash (OR = 1.3, 95% 1.00-1.69). The value of the findings of this study is weakened somewhat by the fact that individuals enrolled in the study were diagnosed with sleep apnea using questionnaires only.

Stoohs et al.(67) assesses a possible independent effect of sleep-related breathing disorders on traffic crashes in long-haul commercial truck drivers (Quality Score: 8.0; Moderate). These investigators found that truck drivers identified with SDB had a two-fold higher crash rate per mile than drivers without SDB. Crash frequency was not dependent on the severity of the sleep-related breathing disorder. Obese drivers with a body mass ≥30 kg/m^2 also presented a two-fold higher crash rate than nonobese drivers. In addition, the authors found that a complaint of EDS was related to a significantly higher automotive crash rate in long-haul commercial truck drivers. SDB with hypoxemia and obesity are risk factors for automotive crashes.

Drivers of Non-CMV

Because data from studies of CMV drivers with OSA are scarce, we deemed it worthwhile to examine relevant data from studies that investigated crash risk associated with OSA among more general driver populations. While the generalizability of the findings of these studies to CMV drivers may not be clear, such findings do at the very least allow one the opportunity to draw evidence-based conclusions about the relationship between OSA and motor vehicle crash risk in general.

- **As a group, drivers with OSA are at an increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder (Strength of Evidence: Strong).**
    - **A precise estimate of the magnitude of this increased risk cannot be determined at the present time.**

  Nine studies (Quality Rating: Low) provided data on the relative incidence of crash among individuals who have OSA and comparable individuals without the disorder. Pooling of these data using a random-effects meta-analysis revealed that the mean crash RR associated with OSA is likely to fall within the range 1.30 to 5.72 (95% CI of random-effects summary effect-size estimate). Thus, if the underlying crash risk for a CMV driver is 0.08 crashes per person-year, the crash risk for a CMV driver with OSA can be expected to be in the range of 0.10 to 0.46 crashes per person-year. A series of sensitivity analyses found that the estimate was robust. While the quality of the studies was not high, the data were qualitatively consistent, making it unlikely that future studies will overturn our finding that individuals with OSA are at increased risk for a motor vehicle crash.

- **A paucity of consistent data precludes one from drawing evidence-based conclusions as to whether there is an increased incidence of OSA among drivers who have experienced a crash when compared with drivers who have not experienced a crash.**

  Two included studies (Quality Rating: Moderate) reported on the difference in the incidence of OSA among individuals who have experienced a crash and comparable individuals who have not experienced a crash. The data from the two included studies were found to be inconsistent, with one study suggesting that OSA increased crash risk, and the other study finding no evidence of an increase or a decrease in crash risk.

Key Question 2: What disease-related factors are associated with an increased motor vehicle crash risk among individuals with OSA?

Our assessment of the evidence pertaining to Key Question 1 demonstrated that drivers with OSA (both commercial and noncommercial) are at a significantly increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder. It should be noted, however, that not all individuals with OSA have the same crash risk: some individuals with the disorder appear to be more prone to crash than others. In this section of the evidence report we attempt to identify the factors that are related to an increased crash risk among individuals with OSA. The identification of such risk factors is important, because it will enable medical examiners to differentiate high-risk individuals from low-risk individuals when making decisions about fitness-to-drive certification.

Identification of Evidence Base

To meet the aims of this section of the evidence report we searched for comparative trials that were designed to identify risk factors for crash among individuals with OSA. The most appropriate study design for identifying such risk factors is the case-control study. In such a study, various characteristics that are suspected of influencing crash risk among individuals with OSA are compared across cohorts of individuals with the disorder who have experienced a crash in a given time period and individuals with OSA who have not. For example, one might reasonably suspect the degree of daytime sleepiness to be associated with crash risk. Consequently, a comparison of ESS scores across the two groups would be used to determine whether ESS scores are higher among individuals who have experienced a crash.

The evidence base identification pathway for Key Question 2 is summarized in Figure 8. Our searches (Appendix A) identified a total of 252 articles that appeared relevant to this key question. Following application of a set of retrieval criteria (Appendix B), 57 full-length articles were retrieved and read in full. Of these 57 retrieved articles, 10 were found to meet the inclusion criteria for Key Question 2 (Appendix C). Table 16 lists these 10 included studies. Table D-2 of Appendix D lists the 47 articles that were retrieved but then excluded from inclusion in the evidence base for Key Question 2 and provides the reason for their exclusion.

Figure 8. Development of Evidence Base for Key Question 2

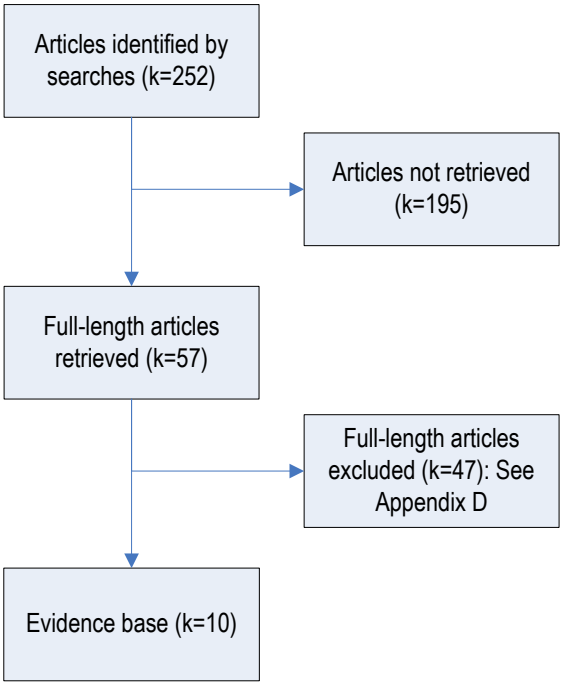


Table 16. Evidence Base for Key Question 2

Reference	Year	Study Location	Country
Commercial Motor Vehicle Drivers			
Stoohs et al.(67)	1994	California	USA
Noncommercial Motor Vehicle Drivers			
Shiomi et al.(71)	2002	Aichi	Japan
Turkington et al.(88)	2001	Leeds	United Kingdom
Horstmann et al.(73)	2000	Bern	Switzerland
Yamamoto et al.(89)	2000	Tokyo	Japan
George and Smiley(75)	1999	Ontario	Canada
Barbe et al.(90)	1998	Barcelona	Spain
Noda et al.(91)	1998	Nagoya	Japan
Engleman et al.(92)	1996	Edinburgh	United Kingdom
Aldrich(81)	1989	Michigan	USA

Evidence Base

This subsection provides a brief description of the key attributes of the 10 studies that comprise the evidence base for Key Question 2. Here we discuss pertinent information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of commercial vehicles. Key characteristics of the 10 included studies that address Key Question 2 are presented in Table 17. More detailed information pertinent to this section is presented in the Study Summary Tables that can be found in Appendix G.

Table 17. Key Study Design Characteristics of Studies that Address Key Question 2

Reference	Year	Study Design	Comparison	Risk Factors Assessed (Method)	Primary Outcome	Definition of Crash	Driving exposure controlled for?
Commercial Motor Vehicle Drivers							
Stoohs et al.(67)	1994	Case-Control Study	46 commercial drivers with sleep-disordered breathing (SDB)	Oxygen Saturation (ODI) BMI	Crashes / 10,000 miles	A motor vehicle crash was defined as the collision of the index case's vehicle with a stationary or moving object or as driving off the road in the absence of an obstacle.	Yes
Noncommercial Motor Vehicle Drivers							
Shiomi et al.(71)	2002	Case-Control Study	448 individuals with OSA-hypopnea syndrome (OSAHS)	Disease Severity (AHI)	Crash rate	Any motor vehicle crash where enrollee was driver.	No
Turkington et al.(93)	2001	Case-Control Study	150 individuals with OSA (OSA)	Sleepiness (ESS) Disease Severity (RDI)	Odds ratio for crashes in the previous year Odds ratio for near-miss crashes in the previous 3 years	Not Reported	No
Horstmann et al.(73)	2000	Case-Control Study	16 individuals with SAS reporting at least one crash compared to 114 individuals with SAS reporting no crashes	Sleepiness (ESS) Disease Severity (AHI) BMI	ESS score AHI BMI	All reported crashes were subdivided into those with property damage <$600 and into those with property damage >$600 or personal injury.	Yes
Yamamoto et al.(89)	2000	Case-Control Study	13 individuals with OSA reporting at least one crash compared to 26 individuals with OSA reporting no crashes	Sleepiness (ESS) Disease Severity (AHI) Oxygen Saturation (SaO_2) BMI	ESS score AHI SaO_2 Minimum SaO_2 BMI	Not Reported	No
George and Smiley(75)	1999	Case-Control Study	460 individuals with OSA	Disease Severity (AHI)	Crash rate	Any motor vehicle crash where enrollee was driver	No
Barbe et al.(90)	1998	Case-Control Study	60 individuals with SAS	Sleepiness (ESS) Disease Severity (AHI) Oxygen Saturation (SaO_2)	Number of crashes	A motor vehicle crash was defined as a crash resulting in property damage >USD 500 and/or personal injury	Yes
Noda et al.(91)	1998	Case-Control Study	44 individuals with OSA syndrome (OSAS)	Sleepiness (ESS) Disease Severity (AHI) Oxygen Saturation (SaO_2)	Correlation between crash score* and ESS score, AHI, and total oxygen desaturation time	Not Reported	No

Reference	Year	Study Design	Comparison	Risk Factors Assessed (Method)	Primary Outcome	Definition of Crash	Driving exposure controlled for?
Engleman et al.(92)	1996	Case-Control Study	204 individuals with sleep apnea/hypopnea syndrome (SAHS)	Disease Severity (AHI) Oxygen Saturation (SaO_2)	Correlation between AHI and minimum SaO_2	Crashes were divided into near-misses, casualty-free ("minor" crashes), and crashes causing injury ("major" crashes)	Yes
Aldrich(81)	1989	Case-Control Study	41 individuals with sleep apnea reporting at least one crash compared to 187 individuals with sleep apnea reporting no crashes	Sleepiness (MSLT) Disease Severity (RDI) Oxygen Saturation (SaO_2)	MSLT score RDI Minimum SaO_2	Any motor vehicle crash or near-miss where enrollee was driver	No

* crash score = 2 points for every one crash and 1 point for every near-miss crash

AHI = Apnea-hypopnea index (number of episodes of apnea-hypopnea per hour of sleep); BMI = Body mass index; ESS = Epworth Sleepiness Scale; MSLT = Multiple sleep latency test; ODI = Oxygen desaturation index (number of abnormal respiratory events associated with an oxygen desaturation ≥3% per hour of sleep); OSA = Obstructive sleep apnea; OSAHS = Obstructive sleep apnea hypopnea syndrome; OSAS = Obstructive sleep apnea syndrome; RDI = Respiratory disturbance index; SAHS = Sleep apnea/hypopnea syndrome; SaO_2 = Oxygen saturation; SDB = Sleep-disordered breathing; USD = United States Dollars.

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Question 2 are presented in Table 18. Complete details of our quality assessment can be found in the Study Summary Tables presented in Appendix G. Our assessment found that the quality of the included studies was not high. One of the 10 included studies was graded as being moderate quality. The remaining nine studies were graded as low quality. Note that even though some studies scored highly, these studies used a case-control design which, by virtue of their retrospective design, is susceptible to bias. Even a perfectly designed and executed case-control study cannot be graded as high quality.

Table 18. Quality of Studies for Key Question 2

Reference	Year	Quality Scale Used	Quality
Stoohs et al.(67)	1994	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Moderate
Shiomi et al.(71)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Turkington et al.(88)	2001	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Horstmann et al.(73)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Yamamoto et al.(89)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
George and Smiley(75)	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Barbe et al.(90)	1998	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Noda et al.(91)	1998	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Engleman et al.(92)	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low
Aldrich, M.S.(81)	1989	Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies	Low

Generalizability of Evidence to Target Population

Important characteristics of the individuals represented in the 10 studies that comprise the evidence base for Key Question 2 are presented in Table 87. The information presented in this table demonstrates that currently available data that are directly generalizable to CMV drivers are extremely limited. Only one included study included a distinct population of CMV drivers.(67) The remainder of the studies included private motor vehicle license holders, an unknown number of whom may have held commercial driver licenses.

The generalizability of the findings of these latter studies to CMV drivers is unclear. Exposure to risk is far lower among noncommercial vehicle drivers, because their driving exposure is lower than that of CMV drivers. Women tend to be overrepresented in studies of general driver populations. In this case, however, the number of males included in the studies of private motor vehicle license holders ranged from 79% to 98%, meaning that gender may not be an issue when considering generalizability of populations. The ages of the private motor vehicle license holders included in these studies are similar to those of CMV drivers. It is unclear whether the ethnicity of the private motor vehicle license holders included in these studies is representative of CMV drivers due to lack of reporting.

Table 19. Individuals with OSA Enrolled in Studies that Address Key Question 2

Reference	Year	Number of Individuals with OSA Included (n =)	Diagnosis (e.g., PSG, questionnaire)	Age Distribution	% Male	% CMV Drivers	Driving Exposure	Ethnicity	Generalizability to Target Population
Commercial Motor Vehicle Drivers									
Stoohs et al.(67)	1994	46 commercial long-haul truck drivers with SDB	Questionnaire and Ambulatory screening device: the Mesam IV	36.5 ±8.7	93	100	NR	NR	Good
Noncommercial Motor Vehicle Drivers									
Shiomi et al.(71)	2002	448 individuals with OSAHS	PSG	49.2 ±14.3	89	NR	NR	NR	Unclear
Turkington et al.(93)	2001	150 individuals with OSA	Sleep study using either the Autoset Clinical 1 or the Densa DMS2000	49.8 ±10.7	83	15% classified themselves as a professional driver	55% drove more than 10,000 miles per year	NR	Unclear
Horstmann et al.(73)	2000	156 individuals with SAS	PSG	56.5 ±10.4	90	NR	Number of drivers (%):130 (83) Mean = 19,416 km/driver/year Median = 15,000 km/driver/year	NR	Unclear
Yamamoto et al.(89)	2000	39 individuals with OSAS	PSG	Individuals with crash 44.1 ±9.9 Individuals without crash 50.4 ±11.0	NR	NR	NR	NR	Unclear
George and Smiley(75)	1999	460 individuals with OSA	PSG	51.0 ±11.9	88	NR	NR	NR	Unclear
Barbe et al.(90)	1998	60 individuals with SAS	PSG	47.1 ±1†	98	NR	27,305 ±2,905 km/year†	NR	Unclear
Noda et al.(91)	1998	44 individuals with OSAS	PSG	60.7 ±8.11	NR	NR	NR	NR	Unclear
Engleman et al.(92)	1996	204 individuals with SAHS	PSG	53 ±10	92	NR	NR	NR	Unclear
Aldrich(81)	1989	228 individuals with sleep apnea	PSG	Males: 50 Females: 54	79	NR	NR	NR	Unclear

Data are expressed as mean ±SD; † Data expressed as means ±SEM; NR = Not reported; OSA = Obstructive sleep apnea; OSAHS = Obstructive sleep apnea-hypopnea syndrome; OSAS = Obstructive sleep apnea syndrome; PSG = Polysomnography; SAHS = Sleep apnea/hypopnea syndrome; SAS = Sleep apnea syndrome; SDB = Sleep disordered breathing.

.

Findings

The individual findings of each of the 10 studies that address Key Question 2 are presented in detail in Appendix G. All of these studies examined several factors caused by OSA that are thought to be associated with an increase an individual's risk for a motor vehicle crash (see Table 88 and Table 21). These factors – all of which serve as surrogate indicators of disease severity — included the presence and degree of daytime sleepiness(73,81,88-91), the severity of disordered respiration during sleep(67,71,73,75,81,88-92), and nighttime SaO_2.(81,89-92) In addition to these three factors, some included studies also examined the relationship between BMI and the risk of a motor vehicle crash.(67,73,89) Although a high BMI is a risk factor for developing OSA, and not a condition caused by OSA, it may also be considered to be a surrogate marker for OSA severity because it is strongly correlated with the severity of the disorder.(94-97) Furthermore, two studies examined the relationship between cognitive and psychomotor functioning and the risk of a motor vehicle crash.(88,90)

Table 20. Independent Risk Factors Assessed

		Potential Risk Factors Examined				
Study	Year	Sleepiness	Severity of Disordered Respiration	Oxygen Saturation	Body Mass Index	Cognitive/ Psychomotor Function
Commercial Motor Vehicle Drivers						
Stoohs et al.(67)	1994		✓		✓	
Noncommercial Motor Vehicle Drivers						
Shiomi et al.(71)	2002		✓			
Turkington et al.(88)	2001	✓	✓			✓
Horstmann et al.(73)	2000	✓	✓		✓	
Yamamoto et al.(89)	2000	✓	✓	✓	✓	
George and Smiley(75)	1999		✓			
Barbe et al.(90)	1998	✓	✓	✓		✓
Noda et al.(91)	1998	✓	✓	✓		
Engleman et al.(92)	1996		✓	✓		
Aldrich(81)	1989	✓	✓	✓		
Number of studies (k =)		6	10	5	3	2

Table 21. Results of Studies that Address Key Question 2

Study	Year	Unit	Risk Factor				
			Sleepiness	AHI or RDI	Oxygen Saturation	Body Mass Index (BMI)	Cognitive/ Psychomotor Function
Commercial Motor Vehicle Drivers							
Stoohs et al.(67)	1994	Crashes / 10,000 miles [mean (SEM)]		**ODI** ODI <20: 0.088 (0.028)[a] ODI ≥20 <30: 0.080 (0.066)[a] ODI >30: 0.082 (0.032)[a]		BMI <25: 0.031 (0.012)[b] BMI ≥25 <28: 0.041 (0.024)[b] BMI ≥28 <30: 0.079 (0.039)[b] BMI ≥32: 0.101 (0.026)[b]	
Noncommercial Motor Vehicle Drivers							
Shiomi et al.(71)	2002	Crashes per driver per year		**AHI** Mild (AHI 5 – 15): 0.012* Moderate (AHI 15 – 30): 0.020* Severe (AHI >30): 0.022*			
Turkington et al.(88)	2001	Odds Ratio for crash in the previous year	**ESS** 1.09 (95% CI: 0.97 – 1.22) p >0.05	**RDI** 1.006 (95% CI: 0.98 – 1.03) p >0.05			**Off-road events** 1.004 (95% CI: 1.0004 – 1.008) p <0.03 **Tracking error** 1.1 (95% CI: 0.79 – 1.53) p >0.05 **Reaction time** 1.1 (95% CI: 0.83 – 1.5) p >0.05
		Odds Ratio for near-miss crash in the previous 3 years	**ESS** 1.15 (95% CI: 1.07 – 1.23) p <0.0001	**RDI** 1.01 (95% CI: 0.99 – 1.03) p >0.05			**Off-road events** 1.003 (95% CI: 0.99 – 1.01) p >0.05 **Tracking error** 1.40 (95% CI: 0.93 – 2.12) p >0.05 **Reaction time** 1.12 (95% CI: 0.87 – 1.44) p >0.05
Horstmann et al.(73)	2000	Drivers with OSA reporting ≥1 crash	**ESS (mean):** 15.1	**AHI (mean)** 45.0		**BMI (mean)** 35.1	
		Drivers with OSA reporting no crash	**ESS (mean)** 12.9 (NS)	**AHI (mean)** 36 (p = 0.05)		**BMI (mean)** 30.9 (p = 0.02)	

Study	Year	Unit	Risk Factor				
			Sleepiness	AHI or RDI	Oxygen Saturation	Body Mass Index (BMI)	Cognitive/ Psychomotor Function
Yamamoto et al.(89)	2000	Drivers with OSA who had a crash	**ESS (mean ±SD)** 14.4 ±4.3	**AHI (mean ±SD)** 60.0 ±17.5	**SaO_2 (%, mean ±SD)** 85.7 ±8.5 **Lowest SaO_2 (%, mean ±SD)** 63.3 ±9.2	**BMI (mean ±SD)** 32.4 ±6.8	
		Drivers with OSA who did not crash	**ESS (mean ±SD)** 12.0 ±5.1 (NS)	**AHI (mean ±SD)** 53.6 ±19.2 (NS)	**SaO_2 (%, mean ±SD)** 86.7 ±8.5 (NS) **Lowest SaO_2 (%, mean ±SD)** 65.1 ±10.5 (NS)	**BMI (mean ±SD)** 28.0 ±4.3 (p <0.05)	
George and Smiley(75)	1999	Crashes per year (mean ±SD)		AHI 10 – 25: 0.08 ±0.12 AHI 26 – 40: 0.06 ±0.14 AHI >40: 0.11 ±0.15			
Barbe et al.(90)	1998	Mean (SEM) number of crashes	**ESS** <25: 0.66 (0.25) [c] 25 – 50: 0.39 (0.25) [c] 50 – 75: 0.72 (0.22) [c] >75: 0.41 (0.19) [c]	**AHI** <25: 0.52 (0.21) [c] 25 – 50: 0.47 (0.19) [c] 50 – 75: 0.57 (0.25) [c] >75: 0.51 (0.22) [c]	**Mean SaO_2 (%)** <25: 0.67 (0.27) [c] 25–50: 0.36 (0.19) [c] 50–75: 0.29 (0.14) [c] >75: 0.54 (0.25) [c] **Time Below 90% SaO_2** 0.48 (0.25) [c] 0.48 (0.24) [c] 0.42 (0.17) [c] 0.62 (0.27) [c]		**Mean reaction time (ms)** <25: 0.45 (0.16) [c] 25–50: 0.55 (0.24) [c] 50–75: 0.48 (0.24) [c] >75: 0.79 (0.30) [c] **Reaction fatigue (1/ms)** <25: 0.92 (0.33) [c] 25–50: 0.40 (0.17) [c] 50–75: 0.45 (0.20) [c] >75: 0.48 (0.18) [c] **% hits (Steer-Clear)** <25: 0.68 (0.25) [c] 25–50: 0.38 (0.22) [c] 50–75: 0.59 (0.23) [c] >75: 0.65 (0.26) [c]
Noda et al.(91)	1998		**ESS** The crash score† was significantly correlated with the ESS score (r = 0.56, p <0.01).	**AHI** There were no significant differences in crash score† among the group with AHI <20, those with 20 ≤AHI <30, and those with AHI ≥30 groups.	The crash score† was significantly correlated with the total oxygen desaturation time (r = 0.46, p <0.05).		

Study	Year	Unit	Risk Factor				
			Sleepiness	AHI or RDI	Oxygen Saturation	Body Mass Index (BMI)	Cognitive/ Psychomotor Function
Engleman et al.(92)	1996	Correlation		**AHI** Sleep-related near-miss crashes: r = 0.15 Nonsleep-related near-miss crashes: r = 0.07 Sleep-related minor crashes: r = 0.06 Nonsleep-related minor crashes: r = -0.01	**Minimum Oxygen Saturation** Sleep-related near-miss crashes: r = -0.25 (p = 0.01) Nonsleep-related near-miss crashes: r = 0.12 Sleep-related minor crashes: r = -0.10 Nonsleep-related minor crashes: r = 0.10		
Aldrich(81)	1989	Drivers with OSA who had a crash	**MSLT** Males: 7.8 minutes Females: 7.6 minutes	**RDI** Males: 49‡ Females: 48	**Mean Minimum Oxygen Saturation (%)** Males: 68‡ Females: 75		
		Drivers with OSA who did not crash	Males: 8.2 minutes Females: 7.3 minutes	Males: 40 Females: 35	Males: 75 Females: 77		

[a] from Stoohs et al.(67), Figure 1; [b] from Stoohs et al.(67), Figure 3; [c] from Barbe et al.(90), Figure 2; *Calculated by ECRI Institute; †crash score = 2 points for every one crash and 1 point for every near-miss crash; ‡ p <0.05 versus male drivers who did not crash; AHI = Apnea-hypopnea index; BMI = Body mass index; ESS = Epworth sleepiness scale; MSLT = Mean latency sleep test; NS = Not statistically significant; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnea; RDI = Respiratory disturbance index; SaO_2 = Oxygen saturation; SD = Standard deviation; SEM = Standard error of mean.

In the following sections we present relevant data for the five potential risk factors (presence and degree of daytime sleepiness, severity of disordered breathing during sleep, nighttime SaO_2, BMI, and cognitive/psychomotor function) for automobile crashes in individuals with OSA. Within each section we present the results of a meta-analysis (if a meta-analysis was possible), followed by a description of the findings of any study not included in the meta-analysis.

Presence and Degree of Daytime Sleepiness

Six included studies reported on the relationship between sleepiness and crash risk among populations of individuals with OSA.(73,81,88-91) The findings of these studies are presented in Table 21.

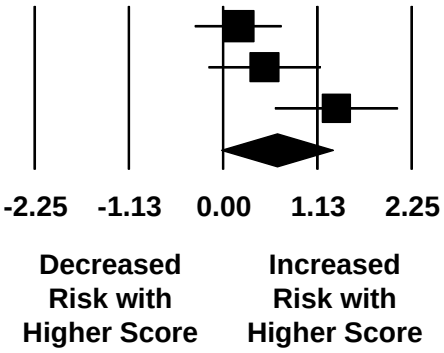
Three of the six included studies (Quality Rating: Low) provided data sufficient for us to calculate an effect-size estimate (and its 95% confidence intervals) which could be pooled using meta-analysis.(73,89,91) All three measured daytime sleepiness subjectively using the ESS. Incomplete reporting of the outcomes of interest to this section of the evidence report precluded us from calculating an effect-size estimate that could be pooled by meta-analysis for the remaining three studies.(81,88,90) Consequently, the findings of the latter studies are discussed separately from the former studies.

A test of homogeneity found that the findings of the three studies for which an effect-size estimate could be calculated were heterogeneous (Q = 6.46, P = 0.040; I^2 = 69.05). Consequently, we did not pool the data from the three studies using a fixed-effects meta-analysis. Because less than 10 studies were available for pooling, we did not attempt to explore the heterogeneity using meta-regression techniques[14]. Pooling of the data using a random-effects meta-analysis (Figure 9) provided some support for the contention that the severity of subjective daytime sleepiness (as measured using the ESS) is a risk factor for a motor vehicle crash in individuals with OSA (SMD = 0.64, 95% CI: -0.03 to 1.30; P = 0.061). The higher the score on the ESS, the more likely an individual is to have experienced a crash. A series of sensitivity analyses (Appendix H) were performed using a random-effects cumulative meta-analysis (cREMA), the results of which indicated that the qualitative findings were not robust (i.e., a statistically significant finding became nonsignificant as studies were added to the evidence base). As a result, there is a possibility that the summary-effect estimate will be substantially altered with the inclusion of future studies.

[14] ECRI requires at least 10 studies for meta-regression or subgroup analysis to be attempted.

Figure 9. Sleepiness and Crash Risk among Individuals with OSA (Random Effects Meta-Analysis)

Study name	Std diff in means	Lower limit	Upper limit	Z-Value	p-Value
Horstmann	0.181	-0.343	0.704	0.676	0.499
Yamamoto	0.494	-0.180	1.169	1.436	0.151
Noda	1.352	0.613	2.091	3.586	0.000
	0.638	-0.028	1.304	1.877	0.061



As stated earlier, three of the six included studies were not included in the above meta-analysis due to incomplete reporting of the outcomes of interest specific to this section of the evidence report. Below we describe the findings of these three additional studies.

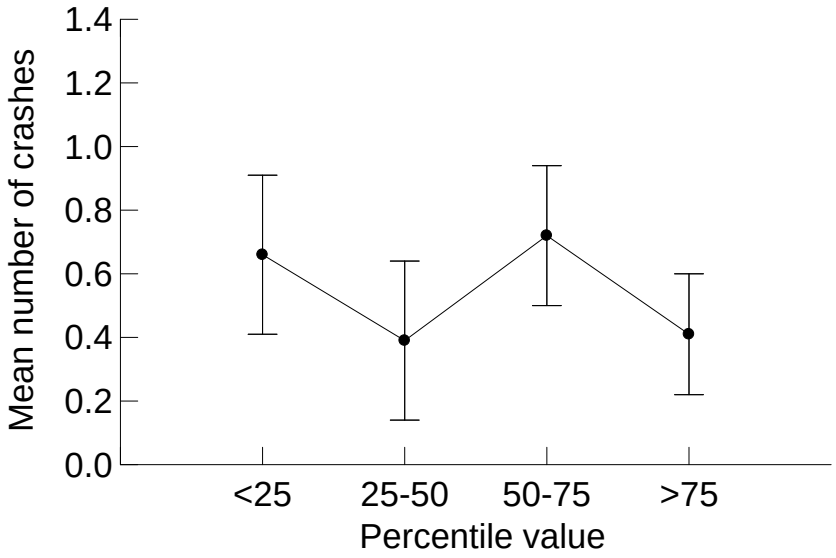
Study of Turkington and Colleagues

Turkington et al.(88) examined the relationship between OSA and risk of road traffic crashes in 150 individuals with OSA (Quality Score: 6.9; Low). Logistic regression analysis was used to investigate sleepiness(as measured using the ESS), and crashes in the previous year, as well as near-miss crashes in the previous three years. They found that the ESS score was associated with near-miss crashes in the previous three years (OR 1.15, 95% CI 1.07 – 1.23, p <0.0001), but not with crashes in the previous year (OR 1.09, 95% CI 0.97 – 1.22, p >0.05).

Study of Barbe and Colleagues

Barbe et al.(90) investigated the association between SAS and automobile crashes as well as potential underlying mechanisms in 60 individuals with SAS (Quality Score: 7.3; Low). One-way analysis of variance was used to investigate the degree of daytime sleepiness, as measured using the ESS, and number of crashes in the previous three years. They found that Epworth score was not related to the number of crashes (Figure 10).

Figure 10. Occurrence of Automobile Crashes in Individuals with SAS according to the Quartile* Distribution of ESS scores



* A higher quartile indicates more abnormal response.

Study of M.S. Aldrich

Aldrich(81) attempted to determine the relative frequency of crashes in individuals with sleep apnea, and whether or not the incidence of crashes was related to the severity of sleep apnea(Quality Score: 6.5; Low). Using the MSLT to objectively measure sleepiness, Aldrich found that there were no significant differences in mean sleep latency between individuals with crashes and those without (males, 8.2 min vs. 7.8 min; females, 7.3 min vs. 7.6 min).

In summary, the results of the small meta-analysis of three studies provided some support for the contention that the severity of subjective daytime sleepiness (as measured using the ESS) is a risk factor for a motor vehicle crash in individuals with OSA. On the other hand, the findings of the three studies not included in the meta-analysis do not provide additional evidence to support the contention that the severity of daytime sleepiness (as measured either subjectively of objectively) is not associated with an increased risk for a motor vehicle crash. Consequently, it remains unclear whether the severity of daytime sleepiness is a risk factor for a motor vehicle crash in individuals with OSA.

Severity of Disordered Respiration During Sleep (AHI or RDI)

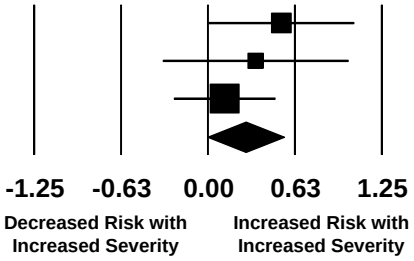
Ten included studies reported on the relationship between disease severity and crash risk among populations of individuals with OSA.(67,71,73,75,81,88-92) The findings of these studies are presented in Table 21.

Three of the 10 included studies (Quality Rating: Low) provided data sufficient for us to calculate an effect-size estimate (and its 95% confidence intervals) that could be pooled using meta-analysis.(73,89,92) All three measured the AHI to quantify the severity of disordered respiration during sleep. Incomplete reporting of the outcomes of interest to this section of the evidence report precluded us from calculating an effect-size estimate that could be pooled by meta-analysis for the remaining seven studies.(67,71,75,81,88,90,91) Consequently, the findings of these latter seven studies are discussed separately from the former three studies.

A test of homogeneity found that the findings of the three studies for which an effect-size estimate could be calculated were homogeneous (Q = 1.6, $P = 0.45$; $I^2 = 0.0$). Consequently, we pooled the data from the three studies using a fixed-effects meta-analysis. Pooling of the data using a fixed-effects meta-analysis (Figure 11) provided support for the contention that the severity of disordered respiration during sleep (as measured using the AHI) is a risk factor for a motor vehicle crash in individuals with OSA (SMD = 0.27, 95% CI: -0.006 to 0.54; P = 0.055). The higher the AHI, the more likely an individual is to have experienced a crash. A series of sensitivity analyses (Appendix H) were performed using a cREMA, the results of which indicated that the qualitative findings were not robust (i.e., a statistically significant finding became nonsignificant as studies were added to the evidence base). As a result, there is a possibility that the summary-effect estimate will be substantially altered with the inclusion of future studies.

Figure 11. Disease Severity and Crash Risk among Individuals with OSA (Fixed-effects Meta-analysis)

Study name	Std diff in means	Lower limit	Upper limit	Z-Value	p-Value
Horstmann	0.528	0.001	1.055	1.964	0.050
Yamamoto	0.343	-0.327	1.013	1.003	0.316
Engleman	0.120	-0.248	0.488	0.641	0.522
Summary Effect Size	0.269	-0.006	0.544	1.915	0.055



As stated earlier, 7 of the 10 included studies were not included in the above meta-analysis due to incomplete reporting of the outcomes of interest specific to this section of the evidence report. Below we describe the findings of these seven excluded studies.

Study of Stoohs and Colleagues

Stoohs et al.(67) examined the relationship between the severity of SDB and automobile crashes in 46 commercial long-haul truck drivers who were diagnosed as having SDB over the past 5 years (Quality Score: 8.0; Moderate). The severity of SDB was classified using the ODI. Individuals were classified as either having mild SDB (ODI ≥10 <20); having moderate SDB (ODI ≥20 <30); or having severe SDB

(ODI >30). The authors found that increasing severity of SDB was not significantly associated with an increase in crash frequency (mild: 0.088 crashes/10,000 miles; moderate: 0.080 crashes/10,000 miles; severe: 0.082 crashes/10,000 miles).

Study of Shiomi and Colleagues

Shiomi et al.(71) examined the relationship between the severity of obstructive sleep apnea-hypopnea syndrome (OSAHS) and automobile crashes in 448 individuals who were diagnosed as having OSAHS over the past 5 years (Quality Score: 5.5; Low). The severity of OSAHS was classified using a clinical parameter (e.g., sleepiness) and a laboratory parameter, which was AHI. Individuals were classified as either having mild OSAHS (AHI 5 to 15); having moderate OSAHS (AHI 15 to 30); or having severe OSAHS (AHI >30). The authors found that automobile crash rate increased with increasing OSAHS severity (mild: 0.012 crashes/driver/year; moderate: 0.020 crashes/driver/year; severe: 0.022 crashes/driver/year). These findings are in agreement with the findings of the small meta-analysis above that there is an increased crash risk with an increase in disease severity.

Study of Turkington and Colleagues

Turkington et al.(88) examined the relationship between OSA and risk of road traffic crashes in 150 individuals with OSA (Quality Score: 6.9; Low). Logistic regression analysis was used to investigate disease severity, as measured with the RDI, crashes in the previous year, and near-miss crashes in the previous three years. The authors found that RDI was not associated with near-miss crashes in the previous three years (OR 1.01, 95% CI 0.99 – 1.03, p >0.05) or with crashes in the previous year (OR 1.006, 95% CI 0.98 – 1.03, p >0.05).

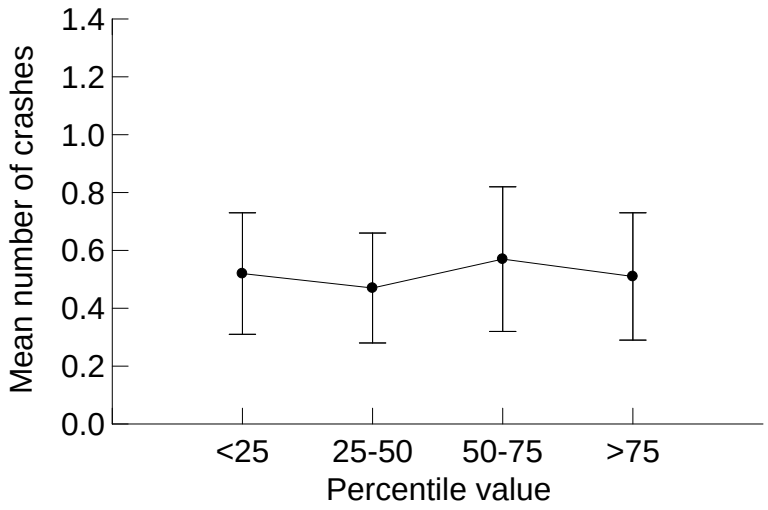
Study of George and Smiley

George and Smiley(75) examined the relationship between the severity of OSA and automobile crashes in 460 individuals who were diagnosed as having OSA over the five years prior to the study (Quality Score: 7.6; Low). The severity of OSA was classified using the AHI. Individuals were classified as either having mild OSA (AHI 10 to 25); having moderate OSA (AHI 26 to 40); or having severe OSA (AHI >40). The authors found that automobile crash rate increased with increasing OSA severity (mild: 0.06 ±0.14 crashes/year; moderate: 0.08 ±0.12 crashes/year; severe: 0.11 ±0.15 crashes/year). These findings are in agreement with the findings of the small meta-analysis above that there is an increased crash risk with an increase in disease severity.

Study of Barbe and Colleagues

Barbe et al.(90) investigated the association between SAS and automobile crashes, and potential underlying mechanisms in 60 individuals with SAS (Quality Score: 7.3; Low). One-way analysis of variance was used to investigate disease severity, as measured using the AHI, and number of crashes in the previous three years. The authors concluded that AHI was not related to the number of crashes (Figure 12).

Figure 12. Occurrence of Automobile Crashes in Individuals with SAS According to the Quartile* Distribution of the AHI



* A higher quartile indicates a more abnormal response.

Study of Noda and Colleagues

Noda et al.(91) examined the relationship between the severity of OSAS and automobile crash score in 44 individuals who were diagnosed as having OSAS (Quality Score: 6.5; Low). Automobile crash score was defined as two points for every one automobile crash and one point for every near-miss crash. The severity of OSA was classified using the AHI. Individuals were classified as either having mild OSAS (AHI<20); having moderate OSAS (20 ≤AHI <30); or having severe OSAS (AHI ≥30). The authors reported that there were no significant differences in crash score among the three groups. Thus, the findings of this study do not lend support to the contention that the severity of disordered respiration is directly associated with increased crash risk.

Study of M.S. Aldrich

Aldrich(81) attempted to determine the relative frequency of crashes in individuals with sleep apnea, and whether the incidence of crashes was related to the severity of sleep apnea (Quality Score: 6.5; Low). Using the RDI to quantify disease severity, Aldrich found that there was a significant difference in the RDI between males with crashes and those without (RDI = 49 vs. 40, $p < 0.05$), but not between females with crashes and those without. It was noted, however, that females who had experienced a crash had a higher RDI compared to those without crashes (RDI = 48 vs. 35).

In summary, the results of a small meta-analysis of data from three studies (30% of the available evidence base) provided some support for the contention that the severity of disordered respiration during sleep (as measured using the AHI) is a risk factor for a motor vehicle crash in individuals with OSA (SMD = 0.27, 95% CI: -0.006 to 0.54; P = 0.055). On the other hand, the findings of the seven studies not included in the meta-analysis were mixed. Three studies found that severity of disordered breathing during sleep was associated with an increased risk for a motor vehicle crash.(71,75,81) The remaining four studies found that severity of disordered breathing during sleep was not associated with an increased risk for a motor vehicle crash.(67,88,90,91) Though the weight of evidence does suggest that the severity of disordered breathing is related to crash risk, a definitive conclusion cannot be drawn at this time.

Oxygen Saturation

Five included studies reported on the relationship between a measure of SaO_2 and crash risk among populations of individuals with OSA.(81,89-92) The findings of these studies are presented in Table 21. Data from these five studies (Quality Rating: Low) were reported using several different methods, and as a result we were precluded from pooling their findings in a meta-analysis. Therefore, the findings from each study are presented separately below.

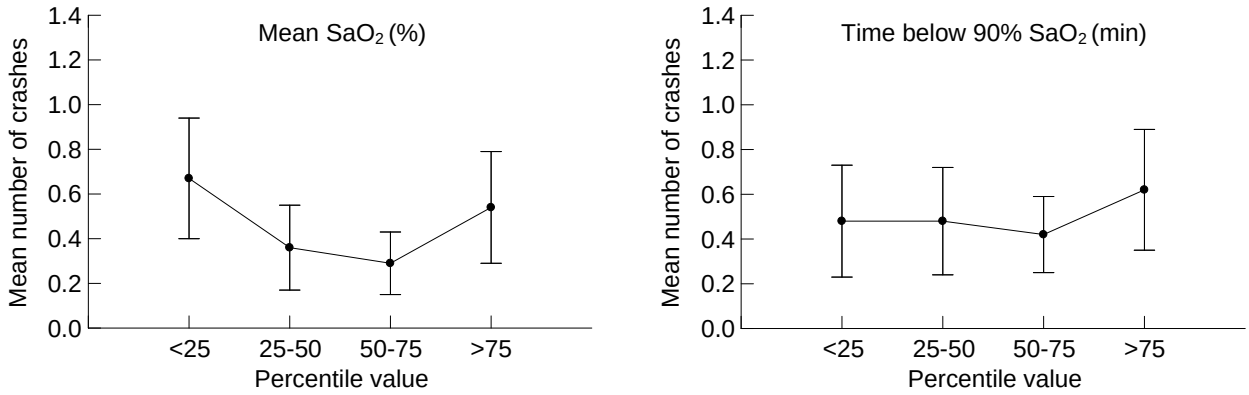
Study of Yamamoto and Colleagues

Yamamoto et al.(89) examined the relationship between SaO_2 and automobile crashes in 39 individuals who were diagnosed as having OSAS (Quality Score: 6.3; Low). Individuals were categorized on the basis of whether or not they had experienced a crash during the previous two years. Mean SaO_2 and lowest SaO_2 were then compared between the two groups. The authors found that individuals who experienced a crash during the previous 2 years had a mean SaO_2 of 85.7% and a lowest SaO_2 of 63.3%, whereas individuals who did not experience a crash had a mean SaO_2 of 86.7% and a lowest SaO_2 of 65.1%. Neither of these differences was statistically significant.

Study of Barbe and Colleagues

Barbe et al.(90) investigated the association between SAS and automobile crashes, and potential underlying mechanisms in 60 individuals with SAS (Quality Score: 7.3; Low). One-way analysis of variance was used to investigate mean SaO_2, as well as time below 90% SaO_2, and number of crashes in the previous 3 years. The authors found that neither outcome was related to the number of crashes (Figure 13).

Figure 13. Occurrence of Automobile Crashes in Individuals with SAS According to the Quartile* Distribution of Mean SaO_2 and Time Below 90% SaO_2.



* A higher quartile indicates a more abnormal response.

Study of Noda and Colleagues

Noda et al.(91) examined the relationship between total SaO_2 time and automobile crash score in 44 individuals who were diagnosed as having OSAS (Quality Score: 6.5; Low). Automobile crash score was defined as two points for every one automobile crash and one point for every near-miss crash. Total SaO_2 time was defined as the time in which SaO_2 was decreased less than 90%. The authors reported that the crash score was significantly correlated with total SaO_2 time ($r = 0.46$, $p < 0.05$).

Study of Engleman and Colleagues

Engleman et al.(92) examined the correlation between minimum SaO_2 and minor crashes, as well as near-miss crashes, in 204 individuals who were diagnosed as having sleep apnea/hypopnea syndrome (SAHS) (Quality Score: 6.3; Low). The authors reported that the frequency of sleep-related near-miss crashes was correlated with the extent of nocturnal hypoxemia ($r = -0.25$, $p = 0.01$).

Study of M.S. Aldrich

Aldrich(81) attempted to determine the relative frequency of crashes in individuals with sleep apnea, and whether or not the incidence of crashes is related to minimum SaO_2 (Quality Score: 6.5; Low). The authors found that there was a significant difference in minimum SaO_2 between males with crashes and those without (minimum SaO_2 = 68% versus 75%, $p < 0.05$), but not between females with crashes and those without. In addition, it was noted that females with crashes had a lower minimum SaO_2 compared to those without crashes (minimum SaO_2 = 75% versus 77%).

In summary, the results of the five studies reporting on some measure of SaO_2 were mixed. Two studies found that total SaO_2 time(91) or nocturnal hypoxemia(92) correlated with crash score(91) or sleep-related near-miss crashes.(92) One study determined that there was no statistical difference between

individuals who experienced a crash and individuals who did not experience a crash with regards to mean SaO_2 and lowest SaO_2.(89) However, the data indicated that individuals who experienced a crash were at higher risk for lower SaO_2 levels. A separate study found that males who experienced a crash had a significantly lower minimum SaO_2 compared to males who did not experience a crash.(81) Finally, one study found that neither mean SaO_2 or time below 90% SaO_2 was related to number of crashes.(90) Taking all of this information into account, it appears that SaO_2 may be a risk factor for a motor vehicle crash in individuals with OSA.

BMI

Three included studies reported on the relationship between BMI and crash risk among populations of individuals with OSA.(67,73,89) The findings of these studies are presented in Table 21.

The number and quality of these three studies (Quality Rating: Low) precluded us from pooling their findings in a meta-analysis. As a result, the findings from each study are presented separately below.

Study of Stoohs and Colleagues

Stoohs et al.(67) examined the relationship between BMI and automobile crashes in 90 commercial long-haul truck drivers (Quality Score: 8.0; Moderate). Individuals were classified into four categories: BMI <25, BMI ≥25 <28, BMI ≥28 <30, and BMI ≥32. Classified drivers whose BMI exceeded ≥30 kg/m^2 were classified as obese. The authors found that automobile crash rate increased with increasing BMI: 0.031 crashes/10,000 miles (BMI <25); 0.041 crashes/10,000 miles (BMI ≥25 <28); 0.079 crashes/10,000 miles (BMI ≥28 <30); and 0.101 crashes/10,000 miles (BMI ≥32). In addition, Stoohs et al. reported that nonobese drivers had a mean of 0.045 crashes/10,000 miles within the last 5 years compared to a mean of 0.1 crashes/10,000 miles ($p < 0.03$) within the last 5 years in obese truck drivers. Using the scores for obesity (≥30 kg/m^2) as a predictor for driving crashes, they found that this predictor had a sensitivity of 49% and a specificity of 71%.

Study of Horstmann and Colleagues

Horstmann et al.(73) examined the relationship between BMI and automobile crashes in 130 individuals who were diagnosed as having SAS (Quality Score: 5.7; Low). Individuals were categorized on the basis of whether or not they had experienced a crash during the previous three years. Mean BMI was then compared between the two groups. The authors found that individuals who experienced a crash during the previous 3 years had a mean BMI of 35.1, whereas individuals who did not experience a crash had a mean BMI of 30.9 ($p = 0.02$).

Study of Yamamoto and Colleagues

Yamamoto et al.(89) examined the relationship between BMI and automobile crashes in 39 individuals who were diagnosed as having OSAS (Quality Score: 6.3; Low). Individuals were categorized on the basis of whether or not they had experienced a crash during the previous two years. Mean BMI was then compared between the two groups. The authors found that individuals who experienced a crash during the previous 2 years had a mean BMI of 32.4, whereas individuals who did not experience a crash had a mean BMI of 28.0 ($p < 0.05$).

In summary, all three studies reporting on BMI and crash risk found that BMI is a risk factor for a motor vehicle crash in individuals with OSA. The higher the BMI, the more likely an individual is to have experienced a crash.

Cognitive and Psychomotor Function

Two included studies reported on the relationship between cognitive/psychomotor function and crash risk among populations of individuals with OSA.(67,73,89) The findings of these studies are presented in Table 21.

The number and quality of these two studies (Quality Rating: Low) precluded us from pooling their findings in a meta-analysis. As a result, the findings from each study are presented separately below.

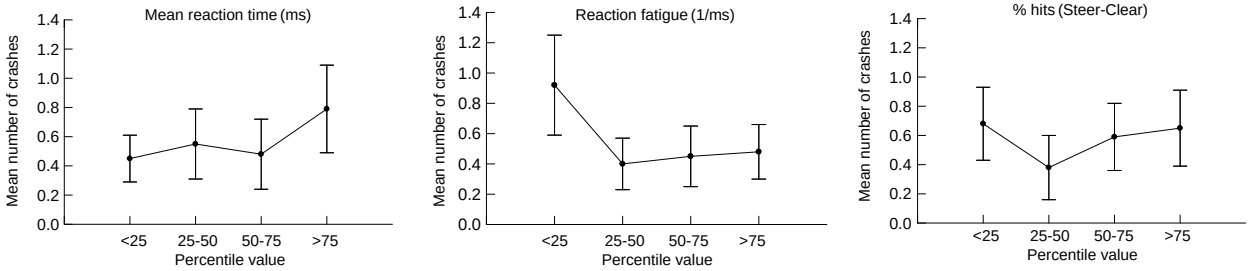
Study of Turkington and Colleagues

Turkington et al.(88) examined the relationship between OSA and risk of road traffic crashes in 150 individuals with OSA (Quality Score: 6.9; Low). Logistic regression analysis was used to investigate off-road events, tracking error, and reaction time (during a 20 minute driving simulation), and crashes in the previous year, as well as near-miss crashes in the previous three years. They found that the number of off-road events was associated with crashes in the previous year (OR 1.004, 95% CI 1.0004 – 1.008, p <0.03), but not with near-miss crashes in the previous three years (OR 1.003, 95% CI 0.99 – 1.01, p >0.05). Tracking error and reaction time were found not to be associated with crashes in the previous year, as well as with near-miss crashes in the previous three years.

Study of Barbe and Colleagues

Barbe et al.(90) investigated the association between SAS and automobile crashes as well as potential underlying mechanisms in 60 individuals with SAS (Quality Score: 7.3; Low). One-way analysis of variance was used to investigate mean reaction time, reaction fatigue, and percentage of hits using Steer-Clear and the number of crashes in the previous three years. They found that mean reaction time, reaction fatigue, and percentage of hits were not related to the number of crashes (Figure 13).

Figure 13. Occurrence of Automobile Crashes in Individuals with SAS According to the Quartile* Distribution of Mean Reaction Time, Reaction Fatigue, and Percentage of Hits



*A higher quartile indicates more abnormal response.

In summary, of the two studies reporting on cognitive and psychomotor function and crash risk, only Turkington et al.(88) found a relationship between the number of off-road events and crashes in the previous year (OR 1.004, 95% CI 1.0004 – 1.008, p <0.03).

Summary of Findings

The findings of our analyses of the data extracted from the 10 included studies that addressed Key Question 2 are presented below:

- **No evidence-based conclusion pertaining to the risk factors for crash among CMV drivers with OSA can be drawn at the present time.**

A single study examined the relationship between several potential risk factors for crash in CMV drivers. Potential risk factors assessed included the presence of EDS (measured using a nonvalidated instrument), severity of SDB (as measured using the ODI) and BMI. The study investigators found that the presence of EDS was associated with an increased crash risk. However, neither the severity of SDB nor BMI were found to be significantly associated with crash risk. Because of the low power of this study to detect the presence of these latter associations, and the fact that an underlying trend suggesting that these factors are associated with crash risk, it cannot be concluded that no association exists (a potential type-II statistical error) based on the findings of this study alone.

- **Four factors have been shown to be associated with crash risk among the general driver population. These factors are the presence and degree of daytime sleepiness (as measured using ESS but not MSLT or MWT), severity of disordered respiration during sleep (as measured by the AHI or the RDI), blood SaO_2 levels, and BMI (Strength of evidence: Minimally Acceptable).**

  A total of nine included studies that enrolled drivers with private motor vehicles addressed Key Question 2. Potential risk factors examined by these studies included BMI, the presence and severity of daytime sleepiness, the severity of disordered respiration, SaO_2, various measures of cognitive and psychomotor function, and measures of depression. Taking the data from all nine studies into account, four factors were found to be associated with crash risk. These factors were the presence and degree of daytime sleepiness (as measured using ESS but not MSLT or MWT), severity of disordered respiration during sleep (as measured by the AHI or the RDI), blood SaO_2 levels, and the BMI. The remaining potential risk factors were not assessed by more than one included study. Consequently, we refrain from drawing evidence based conclusions about the relationship between cognitive and psychomotor function and measures of depression at this time.

Key Question 3: Given the findings of Key Question 2, are individuals with OSA unaware of the presence of the factors that appear to be associated with an increased motor vehicle crash risk?

Our aim in this section of the Evidence Report is to determine whether individuals with OSA are aware of the presence and/or severity of factors that have been shown to be associated with an increased risk for a motor vehicle crash in this population. Our analyses for Key Question 2 identified four such risk factors. These independent factors, which are all associated with the overall severity of the disorder, include the following:

- BMI
- The severity of apnea and hypopnea (as measured using HDI or RDI)
- The presence and severity of SaO_2
- The presence and severity of EDS (as measured by the ESS, MWLT, or MWT)

Key Question 3 is only relevant to one of these four risk factors; it is unrealistic to posit that an obese individual may be unaware of their condition (BMI). Also, it is highly likely that an individual with OSA will be unaware of the number of apneic and hypopneic events that they experience during the night and their SaO_2 levels. Consequently, we confine this question to one risk factor: daytime sleepiness.

An indication that at least some individuals may be unaware of the presence and/or severity of this risk factor for crash comes from the findings of studies of treatments for OSA. Table 22 presents data from a sample of 10 studies of various designs that attempted to assess the effectiveness of a treatment for OSA-related daytime sleepiness through both subjective and objective measures. It should be noted that in most, but not all studies outlined in Table 22, there appears to be some association between impact of treatment on measures of daytime sleepiness that is dependent on whether the outcome was measured subjectively (usually utilizing the ESS) or objectively (usually utilizing the MSLT).

Table 22. Effect of Treatments on Daytime Sleepiness – Agreement between Subjective and Objective Measurements

Study	Findings	Subjective and objective measures agree?
Barnes et al.(98)	Significant improvement seen in ESS with both CPAP and placebo, but no significant difference between the two treatment effects MSLT sleep latency showed no significant improvement with either CPAP or placebo	No
Barbe et al.(99)	No relationship at baseline between ESS and MSLT scores	No
Kingshott et al.(100)	No significant improvement in ESS with Modafinil Significant improvement in daytime sleepiness as measured by MWT with Modafinil No significant improvement in MSLT sleep onset latency with Modafinil	Some
Pack et al.(101)	Modafinil significantly improved subjective daytime sleepiness from baseline levels as measured with ESS at Weeks 1 and 4 ($p < 0.001$) Modafinil significantly improved objective daytime sleepiness from baseline as measured with MSLT at week 4 ($p < 0.05$)	Yes
Chervin et al.(102)	Logistic regression found that objective sleepiness (MSLT) was not associated with frequency of reported sleepiness, fatigue, tiredness, or lack of energy; while subjective sleepiness (ESS) was significantly associated with all but self-reported fatigue No association between MSLT scores and an in-house subjective measure of sleepiness seen	No
Engleman et al.(103)	ESS improved with CPAP MWT showed no difference between placebo and CPAP treatments (ES = 0.19, $p < 0.02$) Subanalysis of treatment effects within the milder severity group (AHI 5-10, n = 14) showed no significant changes in sleepiness outcomes identified (Epworth ES = 0.40, MWT ES = 0.13, both $p < 0.10$)	
Engleman et al.(104)	Improved objective sleepiness was reflected in results for MSLT showing a significant higher improvement for CPAP treated by an average of 2.4 minutes Improvement in MSLT approached normal range Subjective sleepiness was also reduced by six points (95%CI -3 to -9,$p = 0.001$) with CPAP Improvement in ESS score with CPAP also within normal range (6(3))	Yes
Engleman et al.(105)	Neither the MSLT nor the UMACL was significantly improved following CPAP	Yes
Sforza and Lugaresi(106)	The withdrawal of therapy partially reversed the improvement in MSLT. Comparing MSLT after CPAP withdrawal to MSLT just before withdrawal, the average sleep latency abruptly fell from 9.8 to 5.3 minutes even though subjects did not report significant changes in subjective alertness (SSS Mean = 1.8 ±0.1) . The average sleep latency, however, was higher than at baseline ($p = 0.001$). The two variables, however, did exhibit a similar pattern in response to CPAP, but the magnitude of the response differed	No
Barone-Kribbs et al.(107)	MSLT: Withdrawing CPAP resulted in a significant reduction in daytime sleep latency from 5.6 to 2.8 minutes, not significantly different from the pretreatment value. $p = 0.0012$. SSS: No significant difference between On and Off CPAP measurements after Bonferroni correction ($p = 0.0179$), Both the MSLT and SSS scores moved in the direction of improvement while on CPAP and deterioration following its removal. Although the two measures were similarly affected by the addition and later removal of CPAP therapy, the magnitude of this effect differed.	No

CPAP = Continuous positive airway pressure; ES = Excessive sleepiness; ESS = Epworth sleepiness scale; MSLT = Multiple sleep latency test; MWT = Maintenance of wakefulness test; SSS = Stanford sleepiness scale; UMACL = UWIST mood adjective checklist.

While the findings above might lead one to suspect that an individual's subjective judgment of his/her degree of sleepiness may differ from how sleepy he/she actually is, this evidence is clearly circumstantial. One possible explanation for the apparent differences in subjective and objective measures of sleepiness is that they represent the consequences of statistical power differences. If the variance associated with a subjective measure is greater than that associated with an objective measure, it is feasible that one will observe a statistically significant difference in the objective outcome, but not in the subjective outcome, even when the effect-size estimates for both outcomes are actually in concordance. Unfortunately, effect-size estimates are rarely presented and in many cases, and they cannot be calculated due to incomplete reporting. As a consequence, the reader may be left with the incorrect impression that there is at least some degree of a disconnect between subjective and objective measures of daytime sleepiness, and that some individuals may not be able to reliably determine whether, and to what degree, they are in danger of falling asleep at the wheel.

In an attempt to more definitively determine whether judgments by individuals about the presence and severity of daytime sleepiness are reliable, we searched for studies that directly examined this question.

Identification of Evidence Base

The evidence identification pathway for Key Question 3 is presented in Figure 14. Our searches identified a total of 36 articles that appeared relevant to Key Question 3. All 36 articles were retrieved and read in full. Of these 36 articles, 3 were found to meet the inclusion criteria for this question. These three included studies are listed in Table 23. Details of the 31 retrieved articles that did not meet our inclusion criteria are presented in Table D-3 of Appendix D along with the reasons for their exclusion.

Figure 14. Evidence Base Development Process

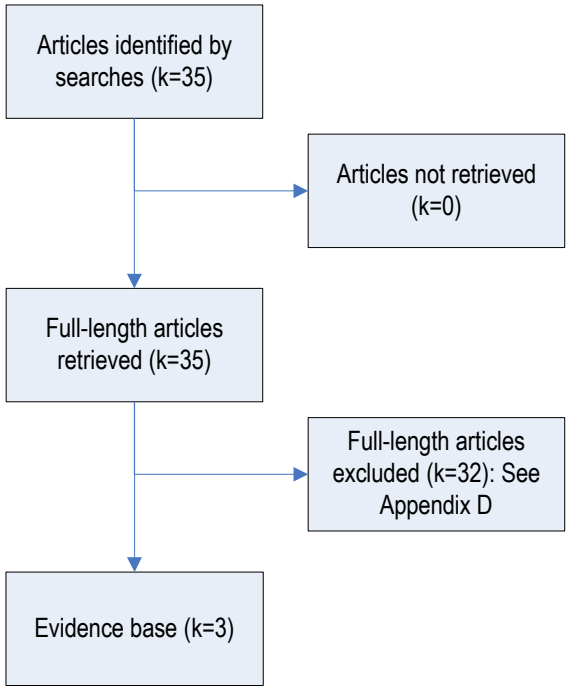


Table 23. Evidence Base

Primary Reference	Year	Study Location	Country
Furuta et al.(108)	1999	Kanazawa	Japan
Engleman et al.(109)	1997	Edinburgh	UK
Kingshott et al.(110)	1995	Edinburgh	UK

Evidence Base

The key attributes of the three studies that met the inclusion criteria for this key question are summarized in Table 26. A more detailed description of each of these studies can be found in the Study Summary Tables of Appendix G.

Each of the three studies that met the inclusion criteria for Key Question 3 addressed the question in a different way. Furuta et al.(108) addressed the question by examining the association between ESS and MSLT scores in a small series (n = 10) of individuals with OSA. The aim of this study was to determine whether an individual with OSA's perception of his/her degree of daytime sleepiness (as measured using the ESS) was analogous to that measured objectively (using the MSLT).

Engleman et al.(109) compared ESS scores obtained from 99 individuals with moderate-to-severe OSA prior to CPAP therapy with those obtained during follow-up (median follow-up time: 22 weeks) at which point enrollees were asked to reassess their treatment naive level of sleepiness. The aim of this study was to determine whether an individual's perception of how sleepy he/she was in the daytime changed as a consequence of a perceived reduction of daytime sleepiness following treatment (a "recalibration" effect).

Kingshott et al.(110) approached the issue from a different direction. Using the ESS, the investigators obtained a subjective measure of daytime sleepiness from a group of 103 individuals with OSA. In addition, the investigators obtained subjective measures of an individual's perceived degree of daytime sleepiness from the participant's partner (also using the ESS). These measures were then compared with each other in order to determine whether the degree of daytime sleepiness as perceived by the individual with OSA differed from that of his/her partner. These data were also compared to objective measures of the severity of OSA as determined by an overnight PSG study. The aim of this comparison was to determine whether the subjective data correlated with disease severity as determined by the polysomnogram results.

Table 24. Key Study Design Characteristics of Studies that Address Key Question 3

Reference	Year	Aim of study	n =	Study design	Prospective?	Study population	Method of Measuring Sleepiness	Method
Furuta et al.(108)	1999	To examine the relationship between the degree of subjective sleepiness and the results of PSG and MSLT in individuals with OSA.	10	Case series	Yes	Individuals with OSAS who had undergone a PSG and MSLT in the sleep disorder clinic.	Subjective - ESS Objective - MSLT	Individuals with OSA assessed using ESS and MSLT. Association between two measures assessed.
Engleman et al.(109)	1997	To determine if individuals with OSA, either through unawareness or fear of consequences, minimize their sleep-related symptoms before starting OSA treatment .	99	Case Series	No	Consecutive individuals with OSA were identified from an alphabetical sleep laboratory registry. Those who had started CPAP treatment within the previous 2 to 70 weeks and were still using CPAP at time contacted by study investigators were enrolled until desired sample size was achieved.	Subjective - ESS	Prior to the initiation of CPAP therapy, subjects completed ESS. ESS readministered at 2 to 70 weeks. Instead of reporting on current status, subjects asked to complete both tests based on how they now assessed their pretreatment symptoms.
Kingshott et al(110)	1995	To determine whose ESS rating, the individual with apnea or their partner's rating, more closely matched with objective measures of disease severity.	103	Case Series	Yes	Individuals referred for assessment for suspected SAHS who were not ultimately diagnosed with narcolepsy, periodic limb movement disorder, or psychologic or psychiatric illness was included.	Subjective - ESS	ESS and OSA severity data collected. Partner's ESS rating of the individual with OSA collected. All data compared.

CPAP = Continuous positive airway pressure; ESS = Epworth sleepiness scale; MSLT = Multiple sleep latency test; PSG = Polysomnogram; OSA = Obstructive sleep apnea; SAHS = Sleep apnea hypopnea score.

Quality of the Evidence Base

The results of our analysis of the overall quality of the evidence base for Key Question 3 are presented in Table 5. This assessment found that the quality of the included studies was in the low-to-moderate range.

Table 25. Quality of Included Studies

Reference	Year	Quality Scale Used	Quality
Furuta et al.(108)	1999	ECRI Institute Quality Checklist for Case-Series	Moderate
Engleman et al.(109)	1997	ECRI Institute Quality Checklist for Before-After Studies	Low
Kingshott et al.(110)	1995	ECRI Institute Quality Checklist for Case-Series	Low

Generalizability of Evidence Base to Target Population

Pertinent information on the characteristics of the individuals enrolled in the three studies that address Key Question 3 is summarized in Table 26. More complete details of the characteristics of the enrollees in these studies are presented in the Study Summary Tables that are to be found in Appendix G.

Table 26. Patient Characteristics

Study	Year	n =	% Male	Age (years)	Severity of Apnea (AHI: events/hour)	BMI (kg/m^2)	% CMV Drivers	Generalizability to CMV Drivers
Furuta et al.(108)	1999	10	90	Mean = 51.7 (SD: 19.0)	Mean = 49.1 (SD: 20.8)	NR	NR	Unknown
Engleman et al.(109)	1997	99	89	Median = 50 (Range = 28-75)	Median = 29	NR	NR	Unknown
Kingshott et al.(110)	1995	30	90	Mean = 53 (SD: 7) Range = 41-68	Mean = 45 (SD: 31) Range = 18-143	NR	NR	Unknown

AHI = Apnea-hypopnea index; BMI = Body mass index; n = Number of subjects in study; NR = Not reported ; SD = Standard deviation.

Whether the findings of the studies that address Key Question 3 can be generalized to CMV drivers with OSA is unclear. However, in keeping with the demographics of the general population of individuals with OSA, all of the included trials enrolled primarily middle aged, obese, male subjects. Enrollees all suffered from moderate-to-severe OSA (as determined by the AHI).

Findings

The findings of the included studies that are pertinent to Key Question 3 are presented in Table 27.

Table 27. Findings of studies that address Key Question 3

Study	Year	n =	Subjective and Objective Measures Compared	Statistic used to Assess Association	Findings
Furuta et al.(108)	1999	10	ESS and MSLT	Spearman rank correlation.	No relationship established between ESS and MSLT scores.
Engleman et al.(109)	1997	99	PSG and questionnaire	Rank correlation between PSG and questionnaire variables to identify determinants of reporting discrepancies.	Pretreatment ESS scores under-rated by 66/89 individuals. 24 subjects with ESS scores under 11 (normal) at pretreatment were later reclassified as sleepy (≥11) when reassessed. 19 subjects admitted to difficulty with sleepiness when driving at pretreatment assessment, 31 reassessed themselves as exhibiting impaired driving ability when retested. Of the original 65 individuals who denied impaired driving at baseline, 16 (25%) later acknowledged that they had, in fact, been compromised their driving ability before treatment with CPAP. Overall, subjects underestimated their degree of sleepiness before restorative treatment.
Kingshott et al.(110)	1995	103	ESS scores of individual with OSA ESS scores reported by partner to individual with OSA	OSA individuals and their partners' ESS scores were compared with a two-tailed Wilcoxon test.	Partner and OSA individual ESS scores not significantly different. There was no association between either subject or partner ESS scores and AHI scores for the group as a whole. Among only those with an AHI >15, subject ESS scores did not correlate with AHI but partners' scores did correlate, albeit weakly.

AHI = Apnea-hypopnea index; CPAP = Continuous positive airway pressure; ESS = Epworth sleepiness scale; MSLT = Multiple sleep latency test; OSA = Obstructive sleep apnea; PSG = Polysomnogram.

Of the three included studies whose main purpose was to assess the relationship between objective and subjective measures of sleepiness, two studies found the two measures to be very dissimilar while the remaining study found some similarity between the two measures.

Furuta et al. found no correlation between ESS and MSLT scores. Three individuals had an ESS of less than 10 but an MSLT of less than 5 minutes, which suggested that there was a disconnect between how sleepy individuals with moderate-to-severe OSA perceived themselves to be as compared to how sleepy they actually were.

Engleman et al. found that when individuals with moderate-to-severe OSA were asked to re-evaluate the degree of sleepiness they had experienced prior to the onset of treatment (measured using the ESS) the pretreatment level of sleepiness was reassessed as being much higher than originally reported. Specifically, Engleman and colleagues found that 66 of 99 enrollees underestimated their degree of sleepiness prior to initiation of treatment. It was hypothesized that these individuals were either so impaired by the disease prior to treatment that they are unable to accurately judge just how symptomatic they were, or, that they feared the possible ramifications of the disorder (such as the possible loss of driving privileges) and misrepresented the severity of their symptoms.(109)

In contrast to the findings of Furuta et al. and Engelman et al. Kingshott et al. compared ESS scores from individuals with OSA with their partner's assessment of their sleepiness, and found that the two scores did not differ significantly from one another. Spousal scores were, however, weakly correlated with AHI, while scores from diseased individuals were not significantly associated with AHI.

Summary of Findings

The findings of our analysis of the data extracted from the three included studies that addressed Key Question 3 are as follows:

- **Individuals with OSA may not be aware of the extent to which they are affected by daytime sleepiness (Strength of Evidence: Minimally Acceptable).**

  Three included studies addressed Key Question 3. One included study found that individuals with moderate-to-severe OSA re-evaluated the degree of sleepiness they had experienced prior to the onset of treatment measured using the ESS; the pretreatment level of sleepiness was reassessed as being much higher than originally reported. Another included study found no correlation between ESS and MSLT scores, suggesting a disconnect between subjective and objective measures of sleepiness. However, the final included study compared ESS scores from individuals with OSA with that estimated by their partner.

Key Question 4: Are there screening/diagnostic tests available that will enable examiners to identify those individuals with OSA who are at an increased risk for a motor vehicle crash?

Background

As demonstrated by our analysis of the data pertaining to Key Question 1, individuals with OSA are at an increased risk for experiencing a motor vehicle crash. Our assessment of the available evidence addressing Key Question 2 found that this increased crash risk is associated with the severity of OSA; the more severe the disorder, the greater the crash risk. More specifically, the evidence suggests that crash risk is correlated with a number of surrogate markers for OSA severity, including AHI, the level of daytime sleepiness, SaO_2, and BMI.

The current reference standard study for diagnosing and determining the severity of OSA is in-laboratory, technician-attended PSG. Among other physiologic parameters such as air flow, heart rate and rhythm, and respiratory effort, PSG assesses all four of the known risk factors for crash listed above. This has led to suggestions that all individuals who wish to be certified to drive a CMV and are suspected of, or diagnosed with, OSA, should undergo overnight PSG at a specialist sleep center. For example, the September 2006 recommendations regarding the evaluation for fitness-for-duty from the Joint Task Force of the American College of Chest Physicians, American College of Occupational Health and Environmental Medicine, and the National Sleep Foundation(23) state that all those wishing to drive a CMV and who are suspected of having sleep apnea should be assessed by a sleep physician and have any diagnosis confirmed by overnight. The recommendations define an individual who is suspected of having OSA as meeting one or more of the following criteria:

1. A sleep history suggestive of OSA (snoring, EDS, witnessed apneas)
2. Two or more of the following:
    a. BMI ≥35 kg/m^2
    b. NC ≥17 inches in men or 16 inches in women
    c. ESS score ≥10
    d. Previous diagnosis of sleep apnea and no information on compliance with treatment

Coupled with these recommendations is a growing awareness among physicians and medical examiners of the danger that OSA poses to transportation safety. Together, these factors will increase the demand for access to sleep labs, which will be difficult to satisfy in the face of an acknowledged shortage of testing facilities. This shortfall may lead to delays in diagnosis and treatment initiation. In addition to the deficit in sleep labs, the cost for a PSG is high, and may limit access to appropriate testing.(15-17) Consequently, alternative strategies to PSG that can detect and measure the severity of the known risk factors for a crash are actively being considered.

One such alternative to PSG is “split-night polysomnography.” The initial diagnostic portion of the study, which is necessary to confirm the presence and severity of OSA , is followed on the same night by CPAP titration. The advantage of a split-night study is a presumed decrease in cost, because the two tests are administered in one night, rather than two. This alternative to the traditional PSG, while potentially faster and more cost effective than full PSG, does not overcome the problems of limited resources; the patient must still attend a sleep lab. Additional alternative testing modalities have been suggested, including clinical prediction models, portable sleep monitoring devices that can be used at home, and the use of various psychometric instruments primarily aimed at measuring sleepiness or attentiveness in the office.

Prediction Models

Several prediction models that utilize specific combinations of clinical symptoms, physical examination, demographics, and anthropometric parameters have been proposed.(32,33) Most currently available models include the following variables: gender, BMI, NC, cephalometry measurements, home oximetry, and ESS score. All of these variables have been shown to be risk factors of OSA. Two examples of such models were presented earlier (see *Background* section).

Portable Sleep Monitoring Devices

Portable sleep monitoring is defined as a sleep study that is performed outside of the setting of a sleep laboratory. The term portable monitoring includes a wide range of devices that can be as complex as PSG (and measure all of the same parameters) or straightforward in that they assess only one parameter, such as SaO_2 (oximetry).

The American Academy of Sleep Medicine (AASM) has defined IV types (levels) of sleep testing based on the environment, technician attendance, and number of parameters recorded (Table 28).(111) Portable sleep monitoring systems are classified as Level II, III, or IV monitoring devices.

Table 28. AASM Sleep Monitor Categories

Category	Portability	Parameters Measured
Level I	In-laboratory attended standard PSG. Measure both respiratory and sleep variables	Minimum 7 parameters: EEG, EOG, chin EMG ECG or heart rate, airflow, respiratory efforts, SaO2
Level II	Comprehensive Portable Full PSG performed in the home Measure both respiratory and sleep variables	Monitors the same channels as level 1 but not in a sleep lab Minimum 7 parameters: EEG, EOG, chin EMG ECG or heart rate, airflow, respiratory efforts, SaO2
Level III	Modified Portable Assessment of cardiorespiratory variables only	Minimum 4 parameters including: ventilation (2 channels of respiratory movements or respiratory movements and airflow), heart rate or ECG and oxygen saturation
Level IV	Portable Single or double parameter recordings	Minimum one parameter, usually oximetry alone or with one other channel such as airflow

ECG = Electrocardiogram; EEG = Electroencephalogram; EMG = Electromyogram; EOG = Electro-oculogram.

A wide variety of Level II to Level IV sleep monitoring systems are currently available in the United States. Most of these systems contain software that allows automatic analysis and scoring of recorded signals.(112)

The potential advantages of home studies include convenience, improved access to testing, lower cost compared with in-laboratory studies, and the familiar sleeping environment afforded to individuals undergoing testing. In some cases, data transfer is made via modem to the laboratory analysis station, where the signal quality can then be assessed and equipment problems quickly addressed if required.(113)

While theoretically the costs of operating portable sleep monitoring devices are lower than laboratory-based programs, many of the currently available devices require set up to take place in a laboratory, or require technical assistance in the home.(16) In the latter case, the costs associated with home monitoring are not much different to those associated with testing in a sleep lab.(114) When one takes into account the fact that portable equipment is more prone to damage and sleep studies are more likely to be inconclusive or fail (meaning that these failed studies will need to be repeated) the costs associated with sleep studies based on portable systems may ultimately exceed those associated with assessment in a sleep lab.

Identification of Evidence Base

The ideal study for addressing Key Question 4 is a large RCT that compares crash rates among individuals with OSA who were certified fit-to-drive based on the findings of the current reference standard (PSG) with crash rates among individuals who were certified fit-to-drive based on the findings of an alternative diagnostic. If crash rates are found to be equivalent and the alternative diagnostic was cheaper and more readily available, one would have a compelling argument for utilizing the alternative diagnostic. Unfortunately, no such study exists. Nor, for ethical reasons, is such a study likely to be performed. As a consequence, one must attempt to address Key Question 4 indirectly.

We know from the findings of Key Question 2 that crash risk is directly proportional to the severity of OSA. Consequently, any model, device, or instrument that measures the severity of the disorder (or some a surrogate marker of OSA severity that is known to be associated with crash risk) can potentially be used by a medical examiner to help identify those individuals with OSA who are at an increased risk for a motor vehicle crash. As noted above, the current reference standard for diagnosing individuals with OSA and determining its severity is a sleep lab evaluation using PSG. In order to address Key Question 4 using this knowledge, we searched for studies that evaluated the ability of any model, device, or instrument to identify individuals with OSA and stratify these individuals on the basis of the severity of the disorder as defined by the current reference standard.

The identification of the evidence base for Key Question 4 is summarized in Figure 15. Our searches (Appendix A) identified a total of 347 articles that appeared to be relevant to this key question. Following application of the retrieval criteria (Appendix B) for this question, 71 full-length articles were retrieved and read in full. Of these 71 articles, 43 articles describing 43 unique studies met the inclusion criteria (Appendix C) for Key Question 4. Table D-4 of Appendix D lists the 28 articles that were retrieved but then excluded and provides the primary reason for their exclusion.

Figure 15. Development of Evidence Base for Key Question 4

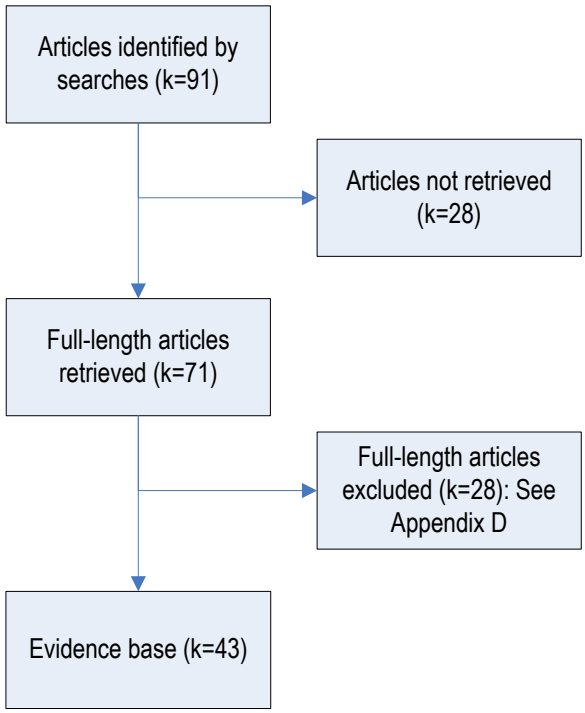


Table 29 lists the 43 articles that met the inclusion criteria for Key Question 4 and shows the diagnostic modality assessed. All 43 included studies measured the diagnostic performance of a portable sleep monitoring system. No included study attempted to measure the diagnostic performance of a clinical model, a psychometric test, or any other relevant diagnostic modality.

Table 29. Included Studies and Diagnostic Tool Assessed

Reference	Year	Clinical Model	Portable Sleep Monitoring System	Psychometric Test	Other
Alvarez et al.(115)	2006		✓		
Michaelson et al.(116)	2006		✓		
Pang et al.(117)	2006		✓		
Yin et al.(118)	2006		✓		
Gurubhagavatula et al.(119)	2004		✓		
Pittman et al.(120)	2004		✓		
Quintana-Gallego et al.(121)	2004	✓	✓		
Su et al.(122)	2004		✓		
Adachi et al.(123)	2003		✓		
Zamarron et al.(124)	2003		✓		
Calleja et al.(125)	2002		✓		
Fietze et al.(112)	2002		✓		
Golpe et al.(126)	2002		✓		
Reichert et al.(16)	2002		✓		
Shochat et al.(114)	2002		✓		
Marrone et al.(127)	2001		✓		
Baltzan et al.(128)	2000		✓		
Vazquez et al.(129)	2000		✓		
Verse et al.(111)	2000		✓		
Chiner et al.(130)	1999		✓		
Mykytyn et al.(131)	1999		✓		
Zamarron et al.(132)	1999		✓		
Mayer et al.(133)	1998		✓		
Gugger et al.(134)	1997		✓		
Parra et al.(17)	1997		✓		
Carrasco et al.(135)	1996		✓		
Esnaola et al.(136)	1996		✓		
Fleury et al.(137)	1996		✓		
Kiely et al.(15)	1996		✓		
Levy et al.(138)	1996		✓		
Lloberes et al.(139)	1996		✓		
Zucconi et al.(140)	1996		✓		

Reference	Year	Clinical Model	Portable Sleep Monitoring System	Psychometric Test	Other
Bradley et al.(141)	1995		✓		
Gugger et al.(142)	1995		✓		
Ryan et al.(143)	1995		✓		
White et al.(113)	1995		✓		
Koziej et al.(144)	1994		✓		
Issa et al.(145)	1993		✓		
Rauscher et al.(146)	1993		✓		
Series et al.(147)	1993		✓		
Douglas et al.(148)	1992		✓		
Stoohs et al.(149)	1992		✓		
Emsellem et al.(150)	1990		✓		
TOTALS		0	43	0	0

Portable Sleep Monitoring Systems

As noted above, all 43 included studies assessed the ability of a portable PSG system to correctly determine disease severity among individuals with OSA. One study addressed Level II portable sleep monitors, 21 studies addressed Level III portable sleep monitors, and 21 studies addressed Level IV sleep monitors (Table 30). The primary characteristics of the 43 studies included studies are presented in Table 31.

Table 30. Evidence Base for Key Question 4

Reference	Year	Study Location	Country
LEVEL 2 Sleep Monitors			
Mykytyn et al.(131)	1999	Repatriation General Hospital, Dawn Park	Australia
LEVEL 3 Sleep Monitors			
Yin et al.(118)	2006	Akita University School of Medicine, Akita	Japan
Pang et al.(117)	2006	Medical College of Georgia, Augusta, Georgia	USA
Quintana-Gallego et al.(121)	2004	Sevilla University, Sevilla	Spain
Shochat et al.(114)	2002	Tel Aviv, Brussels, and Marburg	Israel, Belgium, Germany
Reichert et al.(16)	2002	Sequoia Hospital , Sleep Disorders Center, California	USA
Fietze et al.(112)	2002	Humboldt University of Medical School , Berlin	Germany
Calleja et al.(125)	2002	Alava	Spain
Marrone et al.(127)	2001	Instituto di Fisiopatologia CNR, Palermo	Italy
Verse et al.(111)	2000	University of Ulm, Ulm	Germany
Mayer et al.(133)	1998	Sleep and Respiration Unit, EFCR, Grenoble	France
Gugger et al.(134)	1997	University of Berne, Berne	Switzerland
Parra et al.(17)	1997	Hospital Clinic, University of Barcelona	Spain
Carrasco et al.(135)	1996	Hospital Clinic, University of Barcelona	Spain
Lloberes et al.(139)	1996	Hospital Clinic, University of Barcelona	Spain
Kiely et al.(15)	1996	St.Vincent 's Hospital, Dublin	Ireland
Fleury et al.(137)	1996	Hospital Saint Antoine, Paris	France
Zucconi et al.(140)	1996	State University and RCCS H, Milan	Italy
Bradleyt al.(141)	1995	Royal Infirmary, Respiratory Medicine Unit, Edinburgh	Scotland
Gugger et al.(142)	1995	University of Berne, Berne	Switzerland
White et al.(113)	1995	University of Colorado and V.A. Medical center, Denver	USA
Emsellem et al.(150)	1990	George Washington University Medical Center, Washington DC	USA
LEVEL 4 Sleep Monitors			
Michaelson et al.(116)	2006	Air Force Medical Center, San Antonio ,Texas	USA
Alvarez et al.(115)	2006	Valladolid	Spain
Su et al.(122)	2004	University of Chicago, Chicago, Illinois	USA
Pittman et al.(120)	2004	Harvard Medical School, Boston, MA	USA
Gurubhagavatula et al.(119)	2004	University of Pennsylvania, Philadelphia, Pennsylvania	USA
Zamarron et al.(124)	2003	University of Bellvitge, Barcelona	Spain
Adachi et al.(123)	2003	Osaka University Graduate School of Medicine, Osaka	Japan
Golpe et al.(126)	2002	Marques de Valdecilla University Hospital, Santander	Spain
Vazquez et al.(129)	2000	University of Calgary, Alberta,	Canada
Baltzan et al.(128)	2000	McGill University Health Center, Montreal	Canada

Reference	Year	Study Location	Country
Zamarron et al.(132)	1999	Hospital General de Galicia, Santiago	Spain
Chiner et al.(130)	1999	University Hospital, San Juan de Alicante	Spain
Levy et al.(138)	1996	Joseph Fourier University, Grenoble	France
Esnaola et al.(136)	1996	Hospital Txagorritxu, Vitoria-Gasteiz	Spain
Ryan et al.(143)	1995	City General Hospital, Stoke-on-Trent	England
Koziej et al.(144)	1994	Warsaw	Poland
Series et al.(147)	1993	Hospital Laval, University Laval, Quebec	Canada
Rauscher et al.(146)	1993	Vienna	Austria
Issa et al.(145)	1993	Foothills Hospital, Alberta	Canada
Stoohs et al.(149)	1992	Stanford University Sleep Research Center, Palo Alto, California	USA
Douglas et al.(148)	1992	City Hospital, Edinburgh	Scotland

Table 31. Key Study Design Characteristics of Studies that Address Key Question 4

Reference	Year	Portable System	Study Design	n (% male)	Setting	Assessment of Severity	Reference Standard (PSG)	Participants	Consecutive patients?	Time Between Two Studies
LEVEL 2 SLEEP MONITORS										
Mykytyn et al.(131)	1999	Compumedics PS1	Diagnostic Cohort	20	Lab	AHI	Full night/ 9 parameters	Referrals to sleep laboratory for diagnosis of suspected OSA	N	Simultaneous
LEVEL 3 SLEEP MONITORS										
Mayer et al.(133)	1998	ResMed AutoSet	Diagnostic Cohort	95 (83%)	Lab	AHI	Full night/ 7 parameters	Referrals to one of six sleep labs with suspected OSA	Y	Simultaneous
Gugger et al.(134)	1997	ResMed AutoSet	Diagnostic Cohort	67 (87%)	Lab	AHI	Full night/ 7 parameters	Patients with mean ESS 10 ±0.7 with final diagnosis of obstructive SAHS	Y	Simultaneous
Kiely et al.(15)	1996	ResCare Autoset	Diagnostic Cohort	36 (75%)	Lab	AHI	Full night/ 8 parameters	Consecutive patients scheduled to have clinical sleep studies for evaluation of suspected OSA	Y	Simultaneous
Fleury et al.(137)	1996	AutoSet	Diagnostic Cohort	44 (77%)	Lab	AHI	Full night/ 7 parameters	Heavy snorers with mean age 52 ±11 years; mean BMI 28.5 ±4.4 kg/m^2	Y	Simultaneous
Bradley et al.(141)	1995	ResCare AutoSet	Diagnostic Cohort	31 (84%)	Lab	AI	NR/ 1 parameter	Patients with mean age 46 ±2; mean ESS of 12	Y	Simultaneous
Gugger et al.(142)	1995	Autoset	Diagnostic Cohort	27 (85%)	Lab	AI	Full night/ 7 parameters	Patients with median ESS 10 and 67% with final diagnosis OSA	Y	Simultaneous
Pang et al.(117)	2006	SleepStrip	Diagnostic Cohort	39	Home	AHI	Full night/ 10 parameters	Patients enrolled over a 2-month period at Georgia Sleep Center	Y	1 night
Shocat et al.(114)	2002	SleepStrip	Diagnostic Cohort	402	Lab	AHI	Full night/ 4 parameters	Multicenter trial with 303 patients from Israel, 50 from Belgium, 49 from Germany all suspected of having Sleep Apnea	N	Simultaneous
Yin et al.(118)	2006	Stardust II	Diagnostic Cohort	90	Home	AHI	Full night/ 8 parameters	Japanese adults with suspected OSA with average age 49.2 ±12.5	N	60.8 ±27.7 days
White et al.(113)	1995	Nightwatch	Diagnostic Cohort	2-part study 1) 30 2) 70	1) Lab 2) Home/L	AHI	1) Full 2) Full 8 parameters	Lab study: 15 individuals in 2 sleep centers referred by doctor for suspected OSA Home-Lab Study: 50 participants in Cedars Sinai Sleep Disorders (Los Angeles, CA, USA) and 20 participants at National Jewish/ University of Colorado Sleep Center (Denver, CO, USA)	N	1) Simultaneous 2) 10 days
Calleja et al.(125)	2002	Merlin (L)	Diagnostic Cohort	86 (89%M)	Lab	AHI	Full night/ 9 parameters	Referrals to a sleep lab in Vitoria, Gastiez, Spain with clinical diagnosis of SAS	N	Simultaneous

Reference	Year	Portable System	Study Design	n (% male)	Setting	Assessment of Severity	Reference Standard (PSG)	Participants	Consecutive patients?	Time Between Two Studies
Fietze et al.(112)	2002	Merlin (L)	Diagnostic Cohort	66 (98%M)	Lab	RDI	Full night/ 7 parameters	Referrals from outpatient department because of snoring, daytime sleepiness, or witnessed apneas	N	Simultaneous
Parra et al.(17)	1997	EdenTrace (H)	Diagnostic Cohort	89 (82%M)	Home	AHI	Full night/ 6 parameters	Referrals to Barcelona hospital for evaluation of suspected SAHS	Y	Up to 1 month
Emsellem et al.(150)	1990	EdenTrace (L)	Diagnostic Cohort	67	Lab	PRI	Full night/ 8 parameters	Patients referred to George Washington University Sleep Study Center or Fairview Southdale Hospital Sleep Center with a tentative diagnosis of OSA	Y	Simultaneous
Marrone et al.(127)	2001	PolyMesam (L)	Diagnostic Cohort	50 (80%M)	Lab	AH/TIB	Full night/ 8 parameters	Referrals to a sleep lab in Italy for suspicion of OSAS	Y	Simultaneous
Verse et al.(111)	2000	PolyMesam (L)	Diagnostic Cohort	53 (92%M)	Lab	AHI	Full night/ 10 parameters	Patients with OSA of varying severity	N	NR
Quintana-Gallego et al.(121)	2004	Apnoscreen II	Diagnostic Cohort	90 (87%M)	Home	AHI	Full night/ 8 parameters	Patients with stable heart failure due to systolic dysfunction (LVEF<45%) who were followed at the outpatient clinic of the Service of Cardiology, Virgen del Rocio Hospital, Sevilla, Spain	Y	Within 30 days
Reichert et al.(16)	2003	NovaSom QSG	Diagnostic Cohort	51 (74%)	1) Lab 2) Home	AHI	Full night/ 11 parameters	Patients suspected of having OSA referred by Community Physicians	Y	1) Simultaneous 2) Home for 3 nights either before or after lab
Zucconi et al.(140)	1996	Micro Digitrapper-S	Diagnostic Cohort	30	Lab	AHI	Full night/ 10 parameters	Referrals to Milan San Raffaele Hospital Sleep Disorders Center for habitual snoring and suspected OSA	Y	Simultaneous
Lloberes et al.(139)	1996	Densa Pneumograph	Diagnostic Cohort	76 (71%M)	Respiratory Ward	AHI	Full night/ 6 parameters	Referrals to sleep clinic for evaluation of SAHS during a 3-month period	N	Within 3 weeks
Carrasco et al.(135)	1996	Densa Pneumograph	Diagnostic Cohort	36	Respiratory Ward	AHI	Full night/ 6 parameters	Referrals to sleep clinic for evaluation of SAHS	Y	Within 2 weeks
LEVEL 4 SLEEP MONITORS										
Michaelson et al.(116)	2006	SNAP	Diagnostic Cohort	59	Lab	AHI	Full night/ 6 parameters	Patients presenting to Wilford Hall US Air Force Medical Center Sleep Lab between 6/03 – 8/03	N	Simultaneous

Reference	Year	Portable System	Study Design	n (% male)	Setting	Assessment of Severity	Reference Standard (PSG)	Participants	Consecutive patients?	Time Between Two Studies
Alvarez et al.(115)	2006	Criticare 504 Oximeter	Diagnostic Cohort	187 (79%M)	Lab	CT 90 (cumulative time spent below a saturation of 90%); ODI4 (ODI of 4%); ODI3 (3%), and ODI2 (2%), and Δ index (delta index)	Full night/ 6 parameters	Referral outpatients clinically suspected of OSA	N	Simultaneous
Su et al.(122)	2004	SNAP	Diagnostic Cohort	60 (42%M)	Lab	AHI	Full night/ 10 parameters	Adults referred to University of Chicago Sleep Disorder Clinic from 10/02 – 2/03	Y	Simultaneous
Pittman et al.(120)	2004	Watch PAT 100	Diagnostic Cohort	30	Random settings 1) In-Lab 2) Home-Lab	RDI	Full night/ 10 parameters	Adults referred to the clinical sleep lab at Brigham and Women's Hospital with suspected OSA	N	Both simultaneous and at home within 1 week of each other
Gurubhagavatula et al.(119)	2004	Nocturnal oximetry	Diagnostic Cohort	406 (93%M)	Lab	ODI	Full night/ 8 parameters	Commercial vehicle drivers within 50-mile radius of Philadelphia, PA, USA	N	Simultaneous
Zamarron et al.(124)	2003	Criticare 504 Oximeter	Diagnostic Cohort	300 (78%M)	Lab	Peak in periodgram	Full night/ 6 parameters	Referred outpatients suspected of OSA	N	Simultaneous
Adachi et al.(123)	2003	Pulsox M24	Diagnostic Cohort	33 (88%M)	Lab	PRRI	Full night/ 10 parameters	Referrals to a sleep-disorders unit for suspected OSAHS	Y	Simultaneous
Golpe et al.(126)	2002	Apnoescreen-I	Diagnostic Cohort	55	1) Home 2) Lab	RDI	Full night/ 9 parameters	Patients referred to the Sleep Disorders Unit, University of Cantabria, Santander, Spain	N	Within 30 days
Vazquez et al.(129)	2000	Oximetr	Diagnostic Cohort	245	Lab	RDI	Full night/ 8 parameters	Referrals to Alberta Lung Association Sleep Centre, Alberta, Canada	Y	Simultaneous
Baltzan et al.(128)	2000	OxiFlow	Diagnostic Cohort	108	1) Lab (n ≥86) 2) Home (n ≥66) 3) Both (n ≥55)	RDI	Full night/ 6 parameters	Patients scheduled to undergo PSG in the Royal Victoria Sleep Laboratory between 9/96 – 3/97 with a suspicion of OSA	Y	Simultaneous
Zamarron et al.(132)	1999	Criticare 504 Oximetr	Diagnostic Cohort	240	Lab	Peak amplitude (PA)	Full night/ 6 parameters	Patients clinically suspected of having OSA referred by general practitioners	N	Simultaneous

Reference	Year	Portable System	Study Design	n (% male)	Setting	Assessment of Severity	Reference Standard (PSG)	Participants	Consecutive patients?	Time Between Two Studies
Levy et al.(138)	1996	Biox 3700 or 3740 finger probe	Diagnostic Cohort	301	Lab	Δ index	Full night/ 6 parameters	Patients referred to a regional respiratory lab for suspected sleep-related breathing disorders by GPs, and private and hospital specialists	Y	Simultaneous
Esnaola et al.(136)	1996	MESAM IV	Diagnostic Cohort	150	Lab	HRVI (heart rate variation index), ODI, and ISI (intermittent snoring index)	Full night/ 8 parameters	Patients with clinically suspected OSA referred from 11/91 – 9/93 to sleep unit at Txagorritxu Hospital, Vitoria-Gasteiz, Spain	Y	Simultaneous
Ryan et al.(143)	1995	Pulsox-7	Diagnostic Cohort	100	1) Home 2) Lab	ODI	Full night/ 8 parameters	Referrals to Birmingham Heartlands Hospital Sleep Clinic (UK) with suspected OSAHS	N	NR
Koziej et al.(144)	1994	MESAM 4	Diagnostic Cohort	56 (91%)	Lab	HIS (hand scored index), ODI, HRVI, and ISI	Full night/ 8 parameters	Referrals to sleep lab suspected of a sleep/wake disorder	N	Simultaneous
Series et al.(147)	1993	Biox IVA oximeter	Diagnostic Cohort	240	Home	SaO_2	Full night/ 8 parameters	Referrals to sleep lab with no previous participation in home or sleep lab recordings	Y	Within 1 month
Rauscher et al.(146)	1993	Pulsox 7	Diagnostic Cohort	116	Lab	SaO_2 and pulse rate	Full night/ 7 parameters	Referrals (63% self-referred; 17% by ENT specialist; 14% GP; and 6% other specialists) for investigation of heavy snoring and suspicion of OSA	Y	Simultaneous
Issa et al.(145)	1993	SNORESAT	Diagnostic Cohort	129 (78%)	Lab	RDI	Full night/ 7 parameters	Referrals to University of Calgary Sleep Center, Canada	N	Simultaneous
Stoohs et al.(149)	1992	MESAM 4	Diagnostic Cohort	56	Lab	ODI	Full night/ 9 parameters	Patients seen at the sleep clinic for a sleep/wake-related complaint	N	Simultaneous
Douglas et al.(148)	1992	Ohmeda 3700 oximeter	Diagnostic Cohort	200 (81%)	Lab	ODI	Full night/ 8 parameters	Referrals to Scottish National Sleep Laboratory	Y	Simultaneous
Chiner et al.(130)	1999	N-2000 pulse oximeter	Diagnostic Cohort	275	Lab	ODI	Full night/ 8 parameters	Over a 2 year period consecutive patients studied in a sleep respiratory disorder clinic in San Juan de Alicante, Spain	Y	Simultaneous

AI = Apnea index; AHI = Apnea-hypopnea index; RDI = Respiratory disturbance index; ODI = Oxygen desaturation Index; PRI = Portable respiratory index; PPRI = Pulse rate rise index; AH/TIB = apnea + hypopnea per hour of time in bed; CT90 = Cumulative time spend below a saturation of 90%; SaO_2 ≥Oxygen saturation.

Quality of Included Studies

The findings of our assessment of the quality of the included studies are presented in Table 32. Our assessment found the quality of the included studies to be in the moderate-to-high range. Readers interested in the specifics of our quality assessment should refer to the study summaries found in Appendix G.

Table 32. Quality of the Studies that Address Key Question 4

Reference	Year	Quality Scale Used	Quality
Mykytyn et al.(131)	1999	ECRI Institute Assessment Tool for Diagnostic Studies	High
Yin et al.(118)	2006	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Pang et al.(117)	2006	ECRI Institute Assessment Tool for Diagnostic Studies	High
Quintana-Gallego et al.(121)	2004	ECRI Institute Assessment Tool for Diagnostic Studies	High
Shochat et al.(114)	2002	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Reichert et al.(16)	2003	ECRI Institute Assessment Tool for Diagnostic Studies	High
Fietze et al.(112)	2002	ECRI Institute Assessment Tool for Diagnostic Studies	High
Calleja et al.(125)	2002	ECRI Institute Assessment Tool for Diagnostic Studies	High
Marrone et al.(127)	2001	ECRI Institute Assessment Tool for Diagnostic Studies	High
Verse et al.(111)	2000	ECRI Institute Assessment Tool for Diagnostic Studies	High
Mayer et al.(133)	1998	ECRI Institute Assessment Tool for Diagnostic Studies	High
Gugger et al.(134)	1997	ECRI Institute Assessment Tool for Diagnostic Studies	High
Parra et al.(17)	1997	ECRI Institute Assessment Tool for Diagnostic Studies	High
Carrasco et al.(135)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	High
Lloberes et al.(139)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	High
Kiely et al.(15)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	High
Fleury et al.(137)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	High
Zucconi et al.(140)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	High
Bradley et al.(141)	1995	ECRI Institute Assessment Tool for Diagnostic Studies	High
Gugger et al.(142)	1995	ECRI Institute Assessment Tool for Diagnostic Studies	High
White et al.(113)	1995	ECRI Institute Assessment Tool for Diagnostic Studies	High
Emsellem et al.(150)	1990	ECRI Institute Assessment Tool for Diagnostic Studies	High
Michaelson et al.(116)	2006	ECRI Institute Assessment Tool for Diagnostic Studies	High
Alvarez et al.(115)	2006	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Su et al.(122)	2004	ECRI Institute Assessment Tool for Diagnostic Studies	High
Pittman et al.(120)	2004	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Gurubhagavatula et al.(119)	2004	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Zamarron et al.(124)	2003	ECRI Institute Assessment Tool for Diagnostic Studies	High
Adachi et al.(123)	2003	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate

Reference	Year	Quality Scale Used	Quality
Golpe et al.(126)	2002	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Vazquez et al.(129)	2000	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Baltzan et al.(128)	2000	ECRI Institute Assessment Tool for Diagnostic Studies	High
Zamarron et al.(132)	1999	ECRI Institute Assessment Tool for Diagnostic Studies	High
Chiner et al.(130)	1999	ECRI Institute Assessment Tool for Diagnostic Studies	High
Levy et al.(138)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Esnaola et al.(136)	1996	ECRI Institute Assessment Tool for Diagnostic Studies	High
Ryan et al.(143)	1995	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Koziej et al.(144)	1994	ECRI Institute Assessment Tool for Diagnostic Studies	High
Series et al.(147)	1993	ECRI Institute Assessment Tool for Diagnostic Studies	High
Rauscher et al.(146)	1993	ECRI Institute Assessment Tool for Diagnostic Studies	High
Issa et al.(145)	1993	ECRI Institute Assessment Tool for Diagnostic Studies	Moderate
Stoohs et al.(149)	1992	ECRI Institute Assessment Tool for Diagnostic Studies	High
Douglas et al.(148)	1992	ECRI Institute Assessment Tool for Diagnostic Studies	High

Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that address Key Question 4 are summarized in Table 33. With the exception of one study, the generalizability of the individuals enrolled in the included studies to CMV drivers is unclear. While Gurubhagavatula et al.(119) enrolled only CMV drivers, none of the other studies provided information about the occupation or driving experience of the participants, thus making it difficult to generalize on the basis of employment or driving exposure. CMV drivers in the United States tend to be older (over 40 years of age) and often have a number of comorbidities, including cardiovascular disease, diabetes mellitus, and obesity. This information is often not fully reported, making comparisons in these areas difficult to establish. Historical information on patients and symptoms at study entry were not consistently reported. In the majority of studies, ≥50% were male.

Table 33. Individuals in Studies that Address Key Question 4

Reference	Year	n ≥	Participants	Mean Age (years)	PSG?/ Number of Patients with OSA	Severity (mean AHI)	% Male	% CMV Drivers	Generaliza -bility to CMV Population
LEVEL II Sleep Monitors									
Mykytyn et al.(131)	1999	20	Referrals	Attended (46 ±5.4) Unattended (54 ±2.7)	10	Mild (15-25) n≥4 Moderate (26-40) n≥1 Severe (≥40) n≥5	100	NR	Unknown
LEVEL III Sleep Monitors									
Yin et al.(118)	2006	90	Referrals	49 ±12.5	NR	3.7 ±13.1	84	NR	Unknown
Pang et al.(117)	2006	39	NR	52 ±1 2.2	NR	32.1 ±20.2	44	NR	Unknown
Quintana-Gallego et al.(121)	2004	90	Out-patients, Cardiology clinic	56 ±11.7	59	11.6 ±14	87	NR	Unknown
Shochat et al.(114)	2002	402	NR	Range:18-86	NR	NR	NR	NR	Unknown
Reichert et al.(16)	2002	51	Referrals to sleep lab	52 ±21 Range:30-83	20	NR	75	NR	Unknown
Fietze et al.(112)	2002	66	Referrals	51 ±9.9	NR	NR	98	NR	Unknown
Calleja et al.(125)	2002	86	Referrals	52	NR	34.4 ±29.2	89	NR	Unknown
Marrone et al.(127)	2001	50	Referrals	50 ±10.2	42	57.2 ±34.1	80	NR	Unknown
Verse et al.(111)	2000	53	Referrals	48 ±10.8	NR	17.9 ±18.1	92	NR	Unknown
Mayer et al.(133)	1998	95	Referrals	53 ±11.3	71	43.3 ±33.4	83	NR	Unknown
Gugger et al.(134)	1997	67	Referrals	51 ±1	48	26.2 ±2.9	87	NR	Unknown
Parra et al.(17)	1997	89	Referrals	54 ±12	75	34.3 ±25	82	NR	Unknown
Carrasco et al.(135)	1996	36	Referrals	52 ±2 Range:27-62	NR	NR	81	NR	Unknown
Lloberes et al.(139)	1996	76	Referrals	51 ±11 Range:24-48	55	AHI <10 n ≥21 AHI 10-20 n ≥14 AHI ≥20 n ≥41	71	NR	Unknown
Kiely et al.(15)	1996	36	Scheduled to have clinical sleep studies	45 ±13	NR	14.5 (18.6)	75	NR	Unknown
Fleury et al.(137)	1996	44	NR	52 ±11	NR	NR	77	NR	Unknown

Reference	Year	n ≥	Participants	Mean Age (years)	PSG?/ Number of Patients with OSA	Severity (mean AHI)	% Male	% CMV Drivers	Generaliza-bility to CMV Population
Zucconi et al.(140)	1996	30	Referrals	53 ±12 Range:23-68	29	9 subjects (AHI ≤5) 19 subjects (AHI ≥10) 11 subjects (AHI ≥40)	69	NR	Unknown
Bradley et al.(141)	1995	31	Not described	46 ±2	NR	25 ±4	84	NR	Unknown
Gugger et al.(142)	1995	27	NR	51 Range: 19-71	18	NR	85	NR	Unknown
White et al.(113)	1995	30	Referrals	51 ±2.9	NR	NR	77	NR	Unknown
Emsellem et al.(150)	1990	67	Referrals	Range: 22-79	NR	NR	NR	NR	Unknown
LEVEL IV Sleep Monitors									
Michaelson et al.(116)	2006	59	NR	37.8 (men) 50 (women)	NR	NR (unsure)	83	NR	Unknown
Alvarez et al.(115)	2006	187	Referrals	58 ±12.84	111	40.07 ±19.64	79	NR	Unknown
Su et al.(122)	2004	60	Referrals	45.2 Range: 19-74	NR	Apnea (28.2 ±59.8) Hypopnea (69.6 ±63.1)	NR	NR	Unknown
Pittman et al.(120)	2004	30	Referrals	43 ±10.8	24	NR	70	NR	Unknown
Gurubhagavatula et al.(119)	2004	406	Suspected OSAHS	44 ±11.2	406	Weighted average % (SE) No OSA 71.9 (2.0) ≥Mild 28.1 (2.0) ≥Moderate 10.5 (1.2) ≤Severe 4.7 (0.8)	93	100	Good
Zamarron et al.(124)	2003	300	Referrals	Range: 21-84	169	40.2 ±22.4	78	NR	Unknown
Adachi et al.(123)	2003	33	Referrals	50 ±13.1 Range:25-69	NR	38.7 ±23.9	NR	NR	Unknown
Golpe et al.(126)	2002	55	Referrals	53	18	52.7 ±13.3	96	NR	Unknown
Vazquez et al.(129)	2000	245	Referrals	45 ±11.3 Range: 19-80	NR	25.6 ±16.8	78	NR	Unknown
Baltzan et al.(118)	2000	108	Referrals	51.8 ±14.6	40	18 ±18.9	74	NR	Unknown
Zamarron et al.(132)	1999	240	Referrals	Range: 21-82	124	2.2 ±2.7	79.5	NR	Unknown
Chiner et al.(130)	1999	275	Referrals	SAHS patients (53 ±10) non-SAHS (48 ±14)	216	15-101 42 ±10	89	NR	Unknown
Levy et al.(138)	1996	301	Referrals	56 ±12	193	NR	NR	NR	Unknown
Esnaola et al.(136)	1996	150	Referrals	57 ±11	90	90 patients AHI ≥10 (43 ±24) 60 patients AHI <10 (2.1 ±2.2)	89	NR	Unknown
Ryan et al.(143)	1995	100	Referrals	48 ±12	22	NR	83	NR	Unknown
Koziez et al.(144)	1994	56	Referrals	47 ±10	37	16-118 55 ±27	91	NR	Unknown

Reference	Year	n ≥	Participants	Mean Age (years)	PSG?/ Number of Patients with OSA	Severity (mean AHI)	% Male	% CMV Drivers	Generaliza -bility to CMV Population
Series et al.(147)	1993	240	Referrals	Range:24-68	110	38.1 ±2.5	90	NR	Unknown
Rauscher et al.(146)	1993	116	Referrals	Snorers 49 ±11.7 OSA 50 ±10.2	89	NR	Snorers 63 OSA 75	NR	Unknown
Issa et al.(145)	1993	129	Referrals	48 ±11.9 Range:18-77	NR	NR	NR	NR	Unknown
Stoohs et al.(149)	1992	56	NR	48 ±11.4	26	RDI (11.3 ±26.9)	82	NR	Unknown
Douglas et al.(148)	1992	200	Referrals	50 ±13	80	NR	82	NR	Unknown

AHI = Apnea-hypopnea index; CMV = Commercial motor vehicle; NR = Not reported; OSA = Obstructive sleep apnea; OSAHS = Obstructive sleep apnea-hypopnea syndrome; PSG = Polysomnogram; RDI = Respiratory disturbance index; SAHS = Sleep apnea/hypopnea score; SE = Sleep efficiency.

Findings

Findings of Study that Enrolled only CMV Drivers

Using PSG as the reference standard, Gurubhagavatula et al.(119) prospectively measured the diagnostic performance of five different strategies for identifying the presence of severe sleep apnea (defined as AHI ≥30 episodes per hour) and, secondarily, the presence of any sleep apnea among 406 commercial drivers. The five strategies assessed were as follows:

1. Symptoms only (score 0 to 4)
2. BMI only
3. Symptoms plus BMI (based on a symptom frequency score obtained from a multivariable model)
4. A two-stage approach with symptoms plus BMI for everyone, followed by oximetry for a subset
5. Oximetry for all participants

Enrollees in this study were selected from participants of a larger study on the determinants of OSA and its neurobehavioral consequences. This larger sample consisted of 1,329 respondents to a questionnaire that had been mailed to 4,286 randomly selected commercial driver's license holders in Pennsylvania (within Philadelphia and its 50-mile radius). The questionnaire asked about age, sex, height, weight, and apnea symptom frequency. After sorting the respondents into two strata (high or low risk for OSA), the investigators performed oximetry and PSG in 406 individuals. To determine whether the sample of survey respondents represented a biased sample of CMV drivers, the study investigators compared the age, sex, and ZIP codes of the participants with those of the nonparticipants. These data for nonparticipants were obtained from the Pennsylvania Driver Licensing Services. Whether demonstrating comparability across three parameters is adequate is debatable. Also, while the study investigators noted that the subgroup of enrollees in the study appeared to be representative of all questionnaire respondents, the investigators did not provide details of a comparison of these three characteristics between enrollees and questionnaire nonrespondents (the individuals for which one assumes that age, sex and zip code were obtained from the Pennsylvania Driver Licensing Services since these details were presumably available for all questionnaire respondents). As a consequence, it cannot be assumed that the sample included in this study is representative of all CMV drivers in the sampling area.

Diagnostic Performance of Symptom Score Alone

The study investigators determined the diagnostic performance characteristics of symptom score by computing the area under the curve for receiver operating characteristic (ROC) curves. The optimal sensitivity and specificity, and the associated cut point, were derived by extrapolating from the ROC curve at the point where the slope equaled one. The diagnostic performance characteristics at the optimal cut-off point for this strategy are presented in Table 34.

Table 34. Diagnostic Performance Characteristics at Optimal Cut-off Point

	Prevalence	Cut-point	Sensitivity	Specificity	PPV	NPV
Severe OSA	4.7 (AHI≥30)	0.7	0.61 (0.46–0.84)	0.62 (0.58–0.69)	0.08 (0.05–0.12)	0.97 (0.96–0.99)
Any OSA	28.1 (AHI≥5)	0.7	0.52 (0.43–0.60)	0.69 (0.62–0.75)	0.39 (0.31–0.48)	0.80 (0.74–0.83)

AHI = Apnea-hypopnea index; NPV = Negative predictive value; OSA = Obstructive sleep apnea; PPV = Positive predictive value.

Diagnostic Performance of BMI Alone

The optimal diagnostic performance characteristics associated with BMI alone were determined in the same manner as for the symptom score. These characteristics are presented in Table 35.

Table 35. Diagnostic Performance Characteristics at Optimal Cut-off Point

	Prevalence	Cut-point	Sensitivity	Specificity	PPV	NPV
Severe OSA	4.7 (AHI≥30)	32.7	0.77 (0.53–0.88)	0.71 (0.68–0.77)	0.12 (0.07–0.16)	0.99 (0.97–0.99)
Any OSA	28.1 (AHI≥5)	29.8	0.70 (0.64–0.78)	0.61 (0.54–0.66)	0.41 (0.35–0.47)	0.84 (0.79–0.89)

AHI = Apnea-hypopnea index; NPV = Negative predictive value; OSA = Obstructive sleep apnea; PPV = Positive predictive value.

Diagnostic Performance of Multivariable Model (Symptom Score plus BMI)

For each enrollee, the study investigators determined each respondent's symptom frequency score for apnea (range, 0 to 4) using a multivariable prediction model. This multivariable prediction model combines data on BMI, age, and sex to give a score that falls on a continuous scale between 0 and 1. A score of 0 on this scale represents a low risk for OSA, and a score of 1 represents a highest risk for OSA. The optimal diagnostic performance characteristics of the multivariable model are presented in Table 36.

Table 36. Diagnostic Performance Characteristics at Optimal Cut-off Point

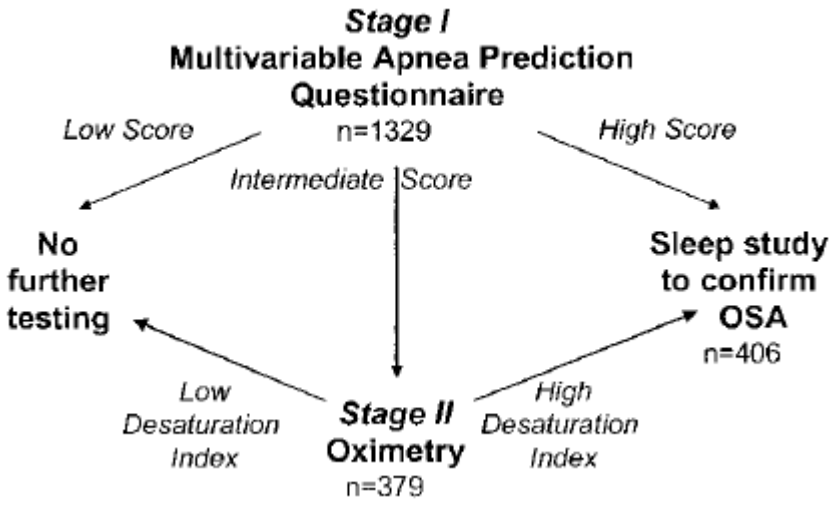
	Prevalence	Cut-point	Sensitivity	Specificity	PPV	NPV
Severe OSA	4.7 (AHI≥30)	0.55	0.81 (0.52–0.91)	0.73 (0.72–0.80)	0.13 (0.08–0.18)	0.99 (0.97–0.99)
Any OSA	28.1 (AHI≥5)	0.5	0.72 (0.66–0.79)	0.76 (0.65–0.76)	0.54 (0.42–0.56)	0.87 (0.83–0.90)

AHI = Apnea-hypopnea index; NPV = Negative predictive value; OSA = Obstructive sleep apnea; PPV = Positive predictive value.

Diagnostic Performance of Two-stage Strategy (Multivariable Model followed by Oximetry in Some)

In this strategy, the study investigators defined two parameters to categorize participant scores into three groups: "upper bound" separated the high predictions from the intermediate predictions, and "lower bound" separated the intermediate predictions from the low predictions. High scorers were predicted to have OSA, with a subsequent review of their PSG to assess this prediction. Intermediate scorers would undergo oximetry; if the ODI equaled or exceeded a third parameter value (the ODI threshold), they would be predicted to have OSA and undergo PSG. Those with low multivariable prediction or an ODI less than the ODI threshold would be predicted not to have OSA (Figure 16).

Figure 16. A Two-stage Strategy for Prediction of Apnea



The optimal diagnostic performance characteristics associated with the two-stage strategy are presented in Table 37.

Table 37. Diagnostic Performance Characteristics at Optimal Cut-off Point

	Prevalence	Cut-point	Sensitivity	Specificity	PPV	NPV
Severe OSA	4.7 (AHI≥30)	0.9, 0.3, 10*	0.91 (0.72–0.97)	0.91 (0.85–0.91)	0.33 (0.19–0.34)	0.99 (0.99–1.00)
Any OSA	28.1 (AHI≥5)	0.9, 0.2, 5*	0.74 (0.61–0.77)	0.89 (0.87–0.94)	0.72 (0.65–0.83)	0.90 (0.85–0.91)

* Upper bound, lower bound, desaturation threshold

AHI = Apnea-hypopnea index; NPV = Negative predictive value; OSA = Obstructive sleep apnea; PPV = Positive predictive value.

Diagnostic Performance of Oximetry Alone

The optimal diagnostic performance characteristics ass ociated with oximetry alone are presented in Table 38.

Table 38. Diagnostic Performance Characteristics at Optimal Cut-off Point

	Prevalence	Cut-point	Sensitivity	Specificity	PPV	NPV
Severe OSA	4.7 (AHI≥30)	14.9	0.89 (0.74–1.00)	0.95 (0.90–0.95)	0.47 (0.26–0.50)	0.99 (0.99–1.00)
Any OSA	28.1 (AHI≥5)	4.95	0.74 (0.67–0.82)	0.89 (0.85–0.93)	0.72 (0.63–0.82)	0.90 (0.87–0.93)

* Upper bound, lower bound, desaturation threshold

AHI = Apnea-hypopnea index; NPV = Negative predictive value; OSA = Obstructive sleep apnea; PPV = Positive predictive value.

Interpretation of Results

While sensitivity and specificity are informative, two more useful measures—especially to physicians—are the positive predictive value (PPV) and the negative predictive value (NPV). The PPV is the probability that an individual who is flagged by a technology as having the disorder of interest will, according to the reference standard, truly have the disorder. The NPV is the probability that an individual who was not flagged by a technology as having the disorder truly does not have the disorder. Unlike the sensitivity and specificity, the PPV and NPV of a test change as the prevalence of disease changes. Thus, PPVs and NPVs calculated in a study where disease prevalence was 10% cannot be generalized to populations that have a different prevalence. One must recalculate a new PPV and NPV while taking into account the prevalence of the disorder of interest within the target population.

Gurubhagavatula et al. did not present the PPV and NPV; however, the study investigators did present sufficient data to allow the calculation of these values. These values, for each of the diagnostic modalities tested, are presented in the tables above (Table 34 through Table 38). Taking the data presented in Table 38 as an example, one can see the result of using oximetry alone to identify individuals with severe OSA. Given the prevalence of OSA in the study (4.7%), 47 out of every 1,000 CMV drivers tested will have severe OSA; the remaining 953 individuals will either have less severe OSA or not have OSA at all.

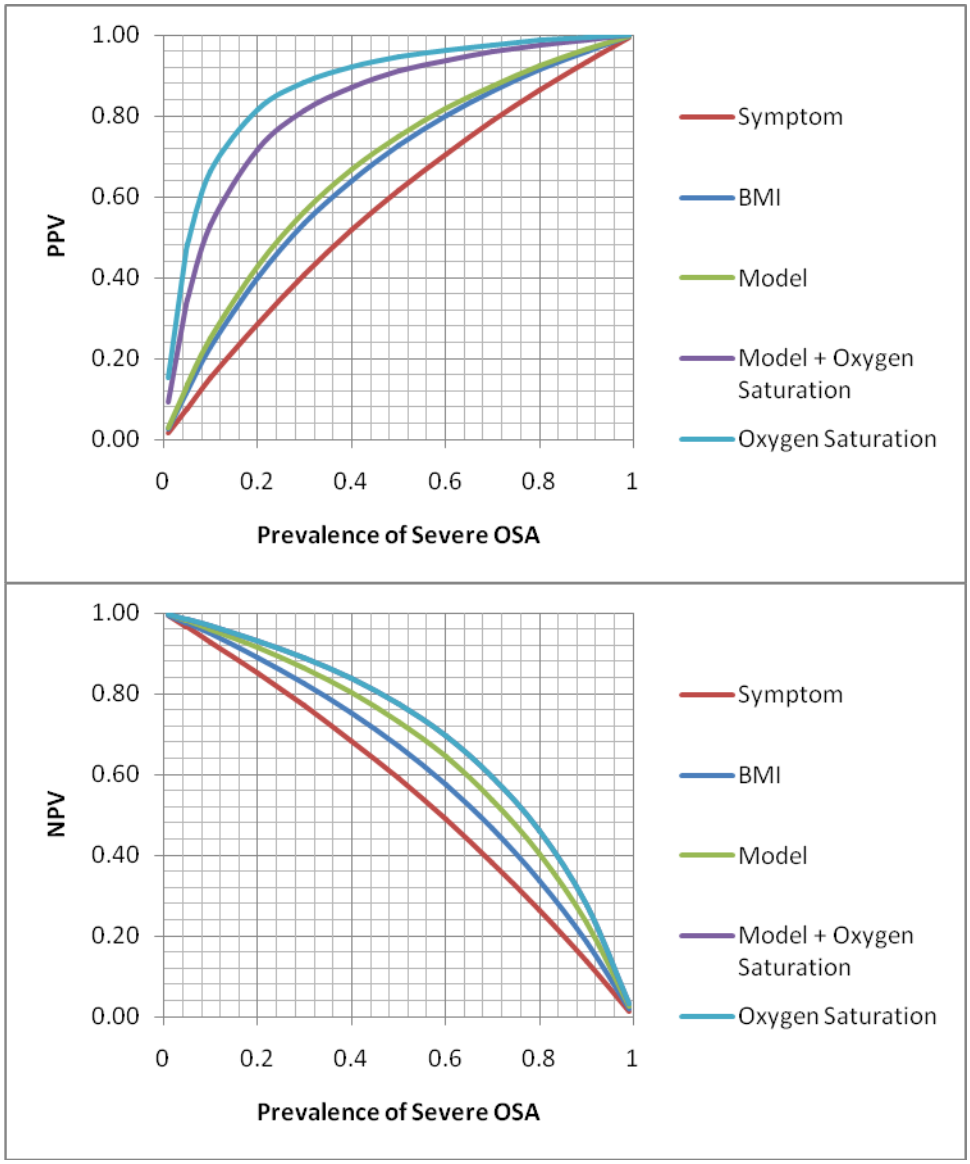
The sensitivity of the test is 0.89. This means that the will test correctly identify 42 of the individuals in the sample as having severe OSA (42 true positives). Five individuals with OSA will be incorrectly determined by the test not to have severe OSA (5 false negatives).

The specificity of the test is 0.95. This means that the test will correctly identify 905 individuals as not having OSA (905 true negatives). The remaining 48 individuals without OSA will be incorrectly identified as having severe OSA.

Given the information above, the total number of positive tests that will occur in the sample is 90. Of these, only 42 will be correct. The probability then of having severe OSA given a positive test result (the PPV) is 42/90 = 0.47. One can see that as the prevalence of disease increases, the PPV will also increase, because the number of false-positive results will decrease and the number of true-positive results will increase. This relationship (and the corresponding relationship for NPV) is shown for each of the modalities examined by Gurubhagavatula et al. in Figure 17.

Using this figure, one can apply the findings of Gurubhagavatula et al. to populations of CMV drivers in which the prevalence of OSA may be different. For example, perhaps one is interested in the PPV of the oximetry modality when it is used in a subpopulation of individuals who are at particularly high risk for severe OSA. In this prescreened population, the underlying prevalence of severe of OSA is approximately 8%. The PPV and NPV of the test when used in this population will be 0.61 and 0.99, respectively.

Figure 17. PPV and NPV as a function of Prevalence of Severe OSA in Target Population



BMI = Body mass index; NPV = Negative predictive value; OSA = Obstructive sleep apnea; PPV = Positive predictive value.

Which Diagnostic Modality is the "Best"

Although we can present details of the diagnostic characteristics of diagnostic devices we are precluded from determining exactly which modality is best. Determining modality as the best is not simply comprised of comparing the sensitivities, specificities, PPVs, and NPVs of each test. Doing so would assume that the costs (economic and societal) associated with a true-positive, a true-negative, a false-positive, and a false-negative decision are equal— a situation that is unlikely to be true. In order to determine the best test, one must develop a decision model that takes into account the diagnostic characteristics of each of the diagnostic tests of interest and the costs that are associated with a true-positive, a true-negative, a false-positive, and a false-negative decision. The analysis and assignment of costs to decisions resulting from the use of a diagnostic test is called utility analysis. Such analysis is central to any decision or policy-making program and falls within the purview of FMCSA's Analysis Division.

Findings of Studies that Enrolled Any Individuals

As noted above, 42 included studies presented diagnostic performance data on some alternative diagnostic modality to a facility-based PSG. The findings of these studies are presented in Table 39.

Table 39. Sensitivity and Specificity of Portable Monitoring Systems Compared with Facility-based and Technician-supported PSG

Reference	Year	n =	Portable System Assessed	Setting	Assessment of Severity	Threshold	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Level 2 Sleep Monitors										
Mykytyn et al.(131)	1999	20	Compumedics PS1	Lab	AHI	AHI ≥10 AHI ≥20	80.0 100.0	90.0 100.0	NR NR	NR NR
Level 3 Sleep Monitors										
Mayer et al.(133)	1998	95	AutoSet	Lab	AHI	AHI ≥5 AHI ≥15 AHI ≥20 AHI ≥30	97.0 92.0 86.0 79.0	50.0 79.0 86.0 93.0	97.0 93.0 93.0 93.0	50.0 76.0 76.0 78.0
Gugger et al.(134)	1997	67	AutoSet	Lab	AHI	AHI ≥20	97.0	77.0	NR	NR
Kiely et al.(15)	1996	36	AutoSet	Lab	AHI	AHI ≥10 AHI ≥15 AHI ≥20	85.0 100.0 88.0	87.0 92.0 93.0	79.0 86.0 78.0	91.0 100.0 96.0
Fleury et al.(137)	1996	44	AutoSet	Lab	AHI	AI ≥5 AI ≥10 AI ≥15 AI ≥20 AI ≥40	100.0 100.0 100.0 100.0 100.0	76.0 87.0 - 880 100.0	NR NR NR NR NR	NR NR NR NR NR
Bradley al.(141)	1995	31	AutoSet	Lab	AI	AHI ≥15	100.0	92.0	92.0	100.0
Gugger et al.(142)	1995	27	AutoSet	Lab	AI	AHI ≥20	82.0	90.0	NR	NR
Pang et al.(117)	2006	39	SleepStrip	Home	AHI	AHI ≥15 AHI ≥25 AHI ≥40	54.6 43.8 33.3	70.0 81.3 95.0	NR NR NR	NR NR NR
Shochat et al.(114)	2002	402	SleepStrip	Lab	AHI	AHI ≥10 AHI ≥20 AHI ≥40	86.0 80.0 80.0	57.0 70.0 86.0	NR NR NR	NR NR NR
Yin et al.(118)	2006	90	Stardust II	Home	AHI	AHI ≥5 AHI ≥15 AHI ≥30 AHI ≥50	100.0 93.8 79.2 90.0	- 25.0 70.0 97.1	93.2 76.9 76.0 90.0	- 60.0 73.7 97.1
White et al.(113)	1995	30	NightWatch	Lab	AHI	AHI ≥10 AHI ≥20	100.0 76.9	63.6 88.2	86.6 83.3	100.0 83.3
		70		Home	AHI	AHI ≥10 AHI ≥20	90.7 86.2	70.4 82.9	86.6 78.8	84.4 89.2
Calleja et al.(125)	2002	86	Merlin	Lab	AHI	AHI ≥5 AHI ≥10 AHI ≥15 AHI ≥20 AHI ≥30	97.1 90.6 90.6 91.1 88.6	90.9 86.7 80.8 85.3 90.9	NR NR NR NR NR	NR NR NR NR NR
Fietze et al.(112)	2002	66	Merlin	Lab	RDI	RDI ≥5 RDI ≥10 RDI ≥15	94.4 83.3 88.5	83.3 86.6 97.5	96.2 88.2 95.8	76.9 81.2 92.9
Parra et al.(17)	1997	89	EdenTrace	Home	AHI	AHI ≥18 AHI ≥8	73.0 95.0	80.0 33.0	NR NR	NR NR

Reference	Year	n =	Portable System Assessed	Setting	Assessment of Severity	Threshold	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Emsellem et al.(150)	1990	67	EdenTrace	Lab	AHI	AHI ≥5	95.0	96.0	NR	NR
Marrone et al.(127)	2001	50	PolyMesam	Lab	AH/TIB	AHI ≥5 AHI ≥10	100.0 95.2	71.4 100.0	95.5 100.0	100.0 80.0
Verse et al.(111)	2000	53	PolyMesam	Lab	AHI	AHI ≥10 AHI ≥15 AHI ≥20	92.0 87.0 71.4	96.3 96.7 96.8	NR NR NR	NR NR NR
Quintana-Gallego et al.(121)	2004	90	Apnoscreen II	Home	AHI	AHI ≥5 AHI ≥10 AHI ≥15	82.5 79.3 68.4	88.6 97.8 94.6	NR NR NR	NR NR NR
Reichert et al.(16)	2003	51	NovaSom QS	Lab	AHI	AHI ≥15	95.0	91.0	91.0	96.0
				Home	AHI	AHI ≥15	91.0	83.0	83.0	91.0
Zucconi et al.(140)	1996	30	MicroDigitrapper	Lab	AHI	AHI ≥10 AHI ≥20 AHI ≥40	100.0 94.0 91.0	100.0 92.0 94.0	100.0 94.0 91.0	100.0 92.0 77.0
Lloberes et al.(139)	1996	76	Densa Pneumograph	Respiratory Ward	AHI	AHI ≥10	82.0	90.0	NR	NR
Carrasco et al.(135)	1996	36	Densa Pneumograph	Respiratory Ward	AHI	AHI ≥20	94.0	82.0	NR	NR
Level 4 Sleep Monitors										
Esnaola et al.(136)	1996	152	Mesam IV	Lab	ODI	AHI ≥5 AHI ≥10 AHI ≥15 AHI ≥20	97.0 98.0 96.0 97.0	19.0 78.0 76.0 70.0	NR NR NR NR	NR NR NR NR
Koziej et al.(144)	1994	56	Mesam IV	Lab (Hand score) Lab (Auto score)	ODI	AHI ≥10 AHI ≥10	100.0 100.0	63.0 27.0	NR NR	NR NR
Stoohs et al.(149)	1992	56	Mesam IV	Lab (Auto score)	ODI	AHI ≥10	92.0	97.0	NR	NR
Michaelson et al.(116)	2006	59	Snap	Lab 1	AHI	AHI ≥5 AHI ≥15	75.0 66.6	96.7 100.0	95.0 100.0	81.0 84.7
				Lab 2	AHI	AHI ≥5 AHI ≥15	94.0 100.0	86.8 88.5	76.0 57.0	97.0 100.0
Su et al.(122)	2004	60	Snap	Lab	RDI	RDI ≥5 RDI ≥10 RDI ≥15	98.0 87.0 83.0	40.0 73.7 75.9	89.1 87.8 78.8	80.0 73.7 81.5
Pittman et al.(120)	2004	30	Watch_ Pat 100	Lab	RDI	RDI ≥10 RDI ≥15 RDI ≥20 RDI ≥30	96.0 91.0 90.0 92.0	100.0 86.0 89.0 82.0	NR NR NR NR	NR NR NR NR
				Home	RDI	RDI ≥10 RDI ≥15 RDI ≥20 RDI ≥30	82.0 96.0 80.0 92.0	100.0 100.0 89.0 82.0	NR NR NR NR	NR NR NR NR
Golpe et al.(126)	2002	55	Aposcreen I	Home	RDI	AHI ≥10	91.0	81.0	NR	NR

Reference	Year	n =	Portable System Assessed	Setting	Assessment of Severity	Threshold	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Baltzan et al.(118)	2000	108	OxiFlow (OF)	Lab	RDI	RDI ≥2 RDI ≥10 RDI ≥15 RDI ≥20 RDI ≥30	97.0 73.0 58.0 43.0 28.0	32 83 93 95 98	NR NR NR NR NR	NR NR NR NR NR
				Home	RDI	RDI ≥2 RDI ≥10 RDI ≥15 RDI ≥20 RDI ≥30	90.0 55.0 34.0 31.0 7.0	32.0 88.0 94.0 97.0 100.0	NR NR NR NR NR	NR NR NR NR NR
Issa et al.(145)	1993	129	SnoreSat	Lab	RDI	RDI ≥7 RDI ≥10 RDI ≥15 RDI ≥20	89.0 84.0 87.0 90.0	95.0 97.0 96.0 98.0	95.0 96.0 93.0 95.0	88.0 88.0 93.0 96.0
Alvarez et al.(115)	2006	187	Oximeter	Lab	ODI	AHI ≥10	90.1	82.9	NR	NR
Gurubhagavatula et al.(119)	2004	406	Oximeter	Lab	≥15 desat/h	AHI ≥5 AHI ≥30	74.0 89.0	89.0 95.0	72.0 47.0	90.0 99.0
Adachi et al.(123)	2003	33	Oximeter	Lab	B-Ar Index	AHI ≥5	88.0	86.0	NR	NR
Zamarron et al.(124)	2003	300	Oximeter	Lab	ODI	AHI ≥10	90.0	82.0	86.0	87.0
Vazquez et al.(129)	2000	245	Oximeter	Lab	RDI ≥15	AHI ≥10 AHI ≥15 AHI ≥20 AHI ≥30	90.0 98.0 100.0 100.0	96.0 88.0 73.0 62.0	NR NR NR NR	NR NR NR NR
Zamarron et al.(132)	1999	240	Oximeter	Lab	ODI	AHI ≥10	78.0	89.0	89.0	78.0
Levy et al.(138)	1996	301	Oximeter	Lab	RDI	RDI ≥15	90.0	75.0	87.0	81.0
Ryan et al.(143)	1995	100	Oximeter	Home	≥15 desat/h	AHI≥15	32.0	100.0	NR	NR
Chiner et al.(130)	1995	275	Oximeter	Lab	ODI ≥5 ODI ≥5 ODI ≥5	AHI ≥15	80.0 71.0 63.0	89.0 93.0 96.0	97.0 97.0 99.0	48.0 42.0 38.0
Series et al.(147)	1993	240	Oximeter	Home		AHI ≥10	98.2	47.7	61.4	96.9
Rauscher et al.(146)	1993	116	Oximeter	Lab		AHI ≥10 AHI ≥20	94.0 95.0	45.0 41.0	NR	NR
Douglas et al.(148)	1992	200	Oximeter	Lab	≥5 ≥10 ≥15 ≥20	AHI ≥15 AHI ≥15 AHI ≥15 AHI ≥15	67.0 53.0 41.0 36.0	92.0 97.0 97.0 99.0	87.0 94.0 92.0 97.0	77.0 71.0 66.0 65.0

AH = Apnea-hypopnea; AHI = Apnea-hypopnea index; AI = Apnea index; desat/h = Desaturations per hour; NPV = Negative predictive value; NR = Not reported; ODI = Oxygen desaturation index; OF = Oxiflow; RDI = Respiratory disturbance index; PPV = Positive predictive value; SEN = Sensitivity; SPE = Specifity; TIB = Time in bed.

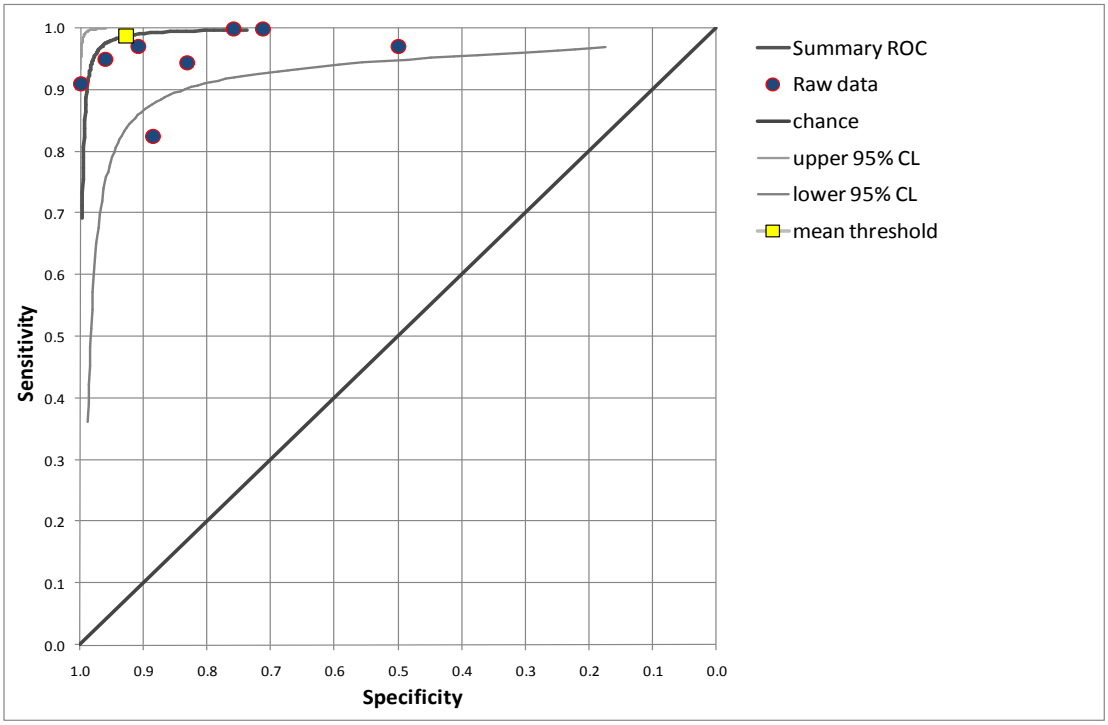
In order to obtain summary estimates of diagnostic performance from the data presented in Table 40, we stratified these data by device level and then by severity of OSA. We then pooled these data using the method of Moses et al.(52,53) (see *Methods* section) and synthesized summary receiver-operating characteristic (SROC) curves for each stratum. To select a point that best represents the overall sensitivity and specificity of the tests utilized, we utilized the mean threshold method proposed by Mitchell et al.(54) The results of these meta-analyses are presented in Table 40 and graphically in Figure 18 through Figure 28.

Table 40. Findings of Meta-Analytic Pooling of Diagnostic Data from Portable Systems

Portable Device Level	Severity	K =	Diagnostic OR (D)	Slope	Homogeneous?	Summary Sensitivity at mean threshold	Summary Specificity at mean threshold	Summary ROC
II	AHI ≥10	1	NC	NC	NA	80.0	90.0	NA
	AHI ≥20	1	NC	NC	NA	100.0	100.0	NA
III	AHI ≥5	8	6.8469	0.047	No	98.8 (95.5-99.7)	92.8 (77.4-98.0)	Figure 18
	AHI ≥10	12	4.2516	-0.34692	No	89.0 (84.0-92.6)	89.9 (85.2-93.3)	CL = Confidence level; ROC = Receiving operator characteristic. Figure 19
	AHI ≥15	11	4.2428	-0.3869	No	90.2 (84.8-93.8)	87.0 (80.3-91.7)	CL = Confidence level; ROC = Receiving operator characteristic. Figure 20
	AHI ≥20	12	4.0601	-0.0394	No	89.5 (86.4-91.9)	87.1 (83.5-90.0)	Figure 21
	AHI ≥25	1	NC	NC	No	44.0	81.0	NA
	AHI ≥30	3	3.1918	-1.0407	No	83.2 (69.4-91.6)	87.0 (75.3-93.6)	Figure 22
	AHI ≥35	0	NA	NA	NA	NA	NA	NA
	AHI ≥40	4	5.6825	0.7383	No	82.7 (58.9-94.1)	95.4 (86.2-98.6)	Figure 23
IV	AHI ≥5	7	4.0245	-0.2613	No	90.0 (86.8-92.5)	84.4 (79.7-88.1)	Figure 24
	AHI ≥10	17	4.3044	-0.2540	No	92.1 (89.5-94.1)	83.7 (78.9-87.6)	Figure 25
	AHI ≥15	15	4.2310	0.1045	No	84.5 (79.4-88.6)	92.1 (89.1-94.3)	Figure 26
	AHI ≥20	7	4.4236	0.3255	No	87.6 (82.0-91.6)	91.2 (87.6-94.2)	Figure 27
	AHI ≥25	0	NA	NA	NA	NA	NA	NA
	AHI ≥30	5	3.9701	0.1574	No	64.6 (54.9-73.2)	95.2 (93.0-96.8)	Figure 28
	AHI ≥35	0	NA	NA	NA	NA	NA	NA
	AHI ≥40	0	NA	NA	NA	NA	NA	NA

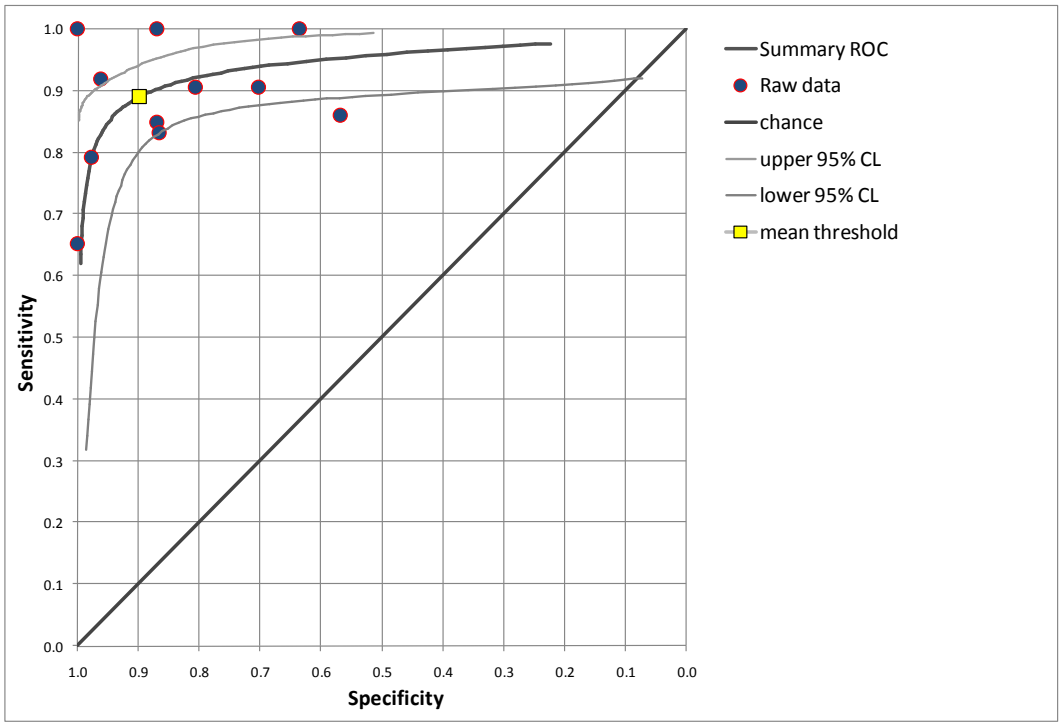
NA = Not applicable; NC = Not calculated.

Figure 18. SROC-Level III Portable Systems (Threshold AHI ≥5)



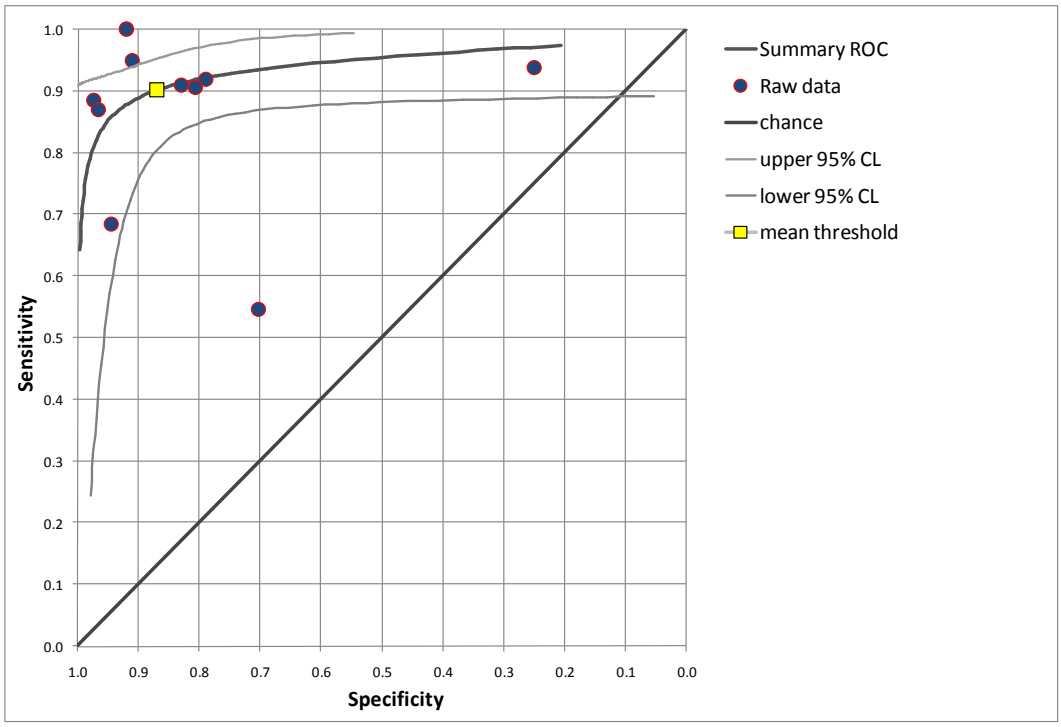
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 19. SROC-Level III Portable Systems (Threshold AHI ≥10)



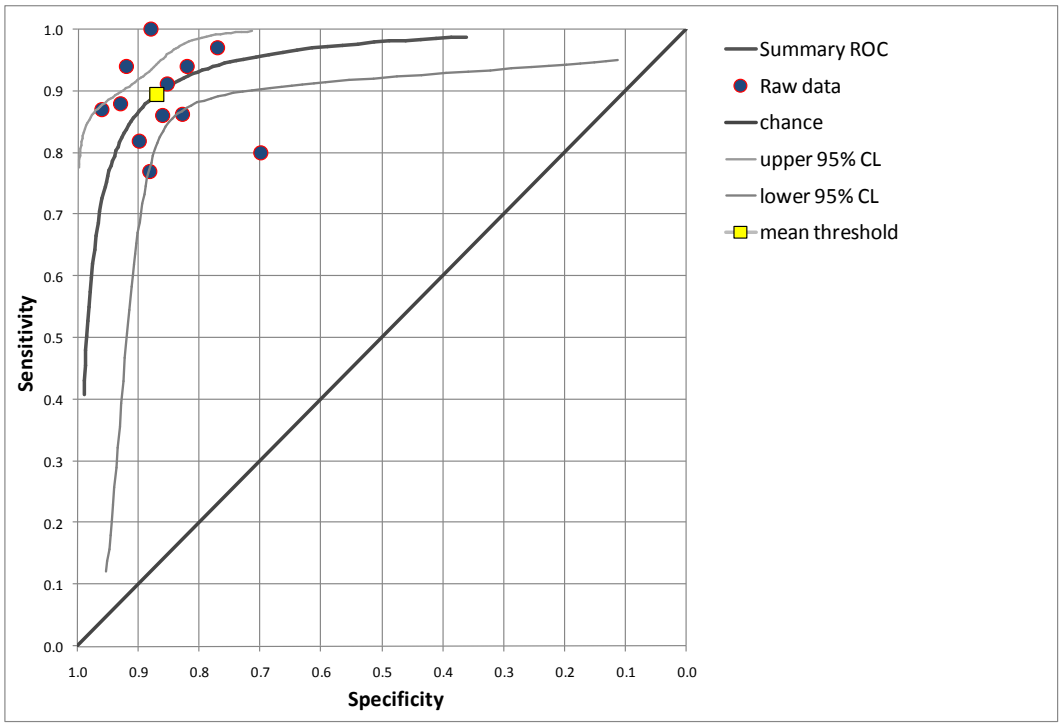
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 20. SROC-Level III Portable Systems (Threshold AHI ≥15)



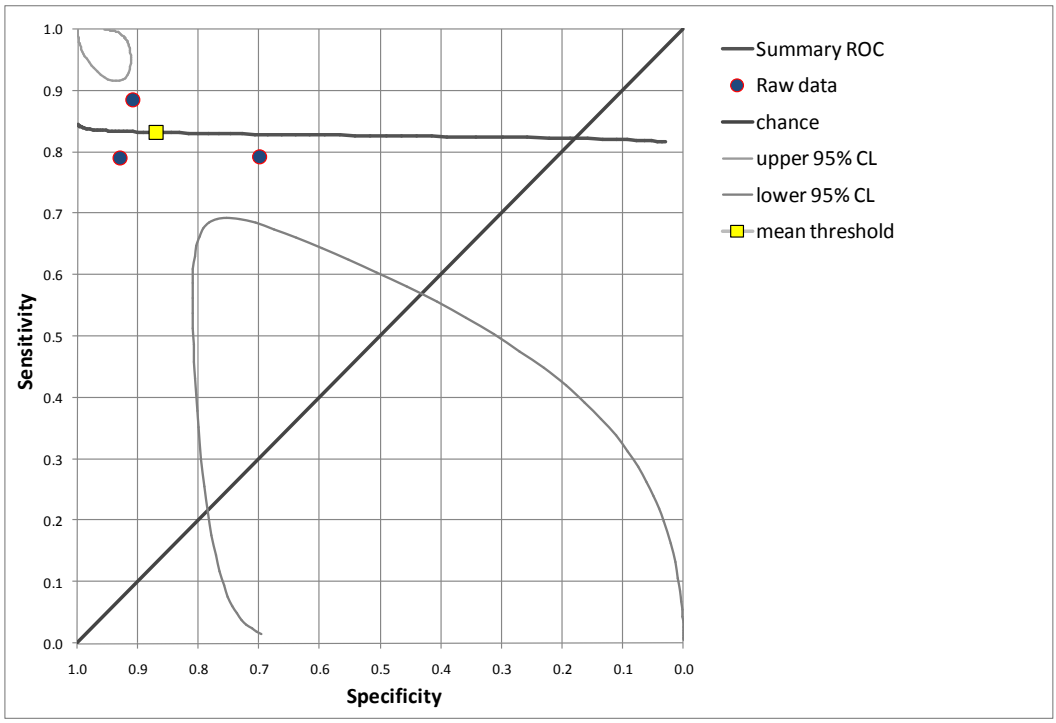
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 21. SROC-Level III Portable Systems (Threshold AHI ≥20)



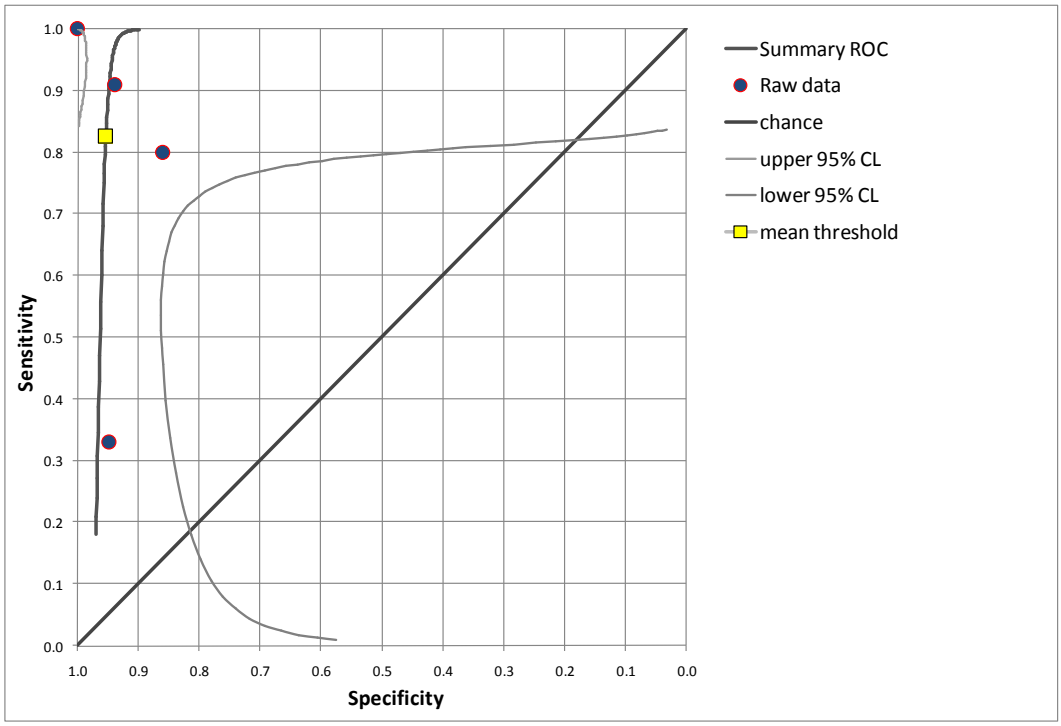
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 22. SROC-Level III Portable Systems (Threshold AHI ≥30)



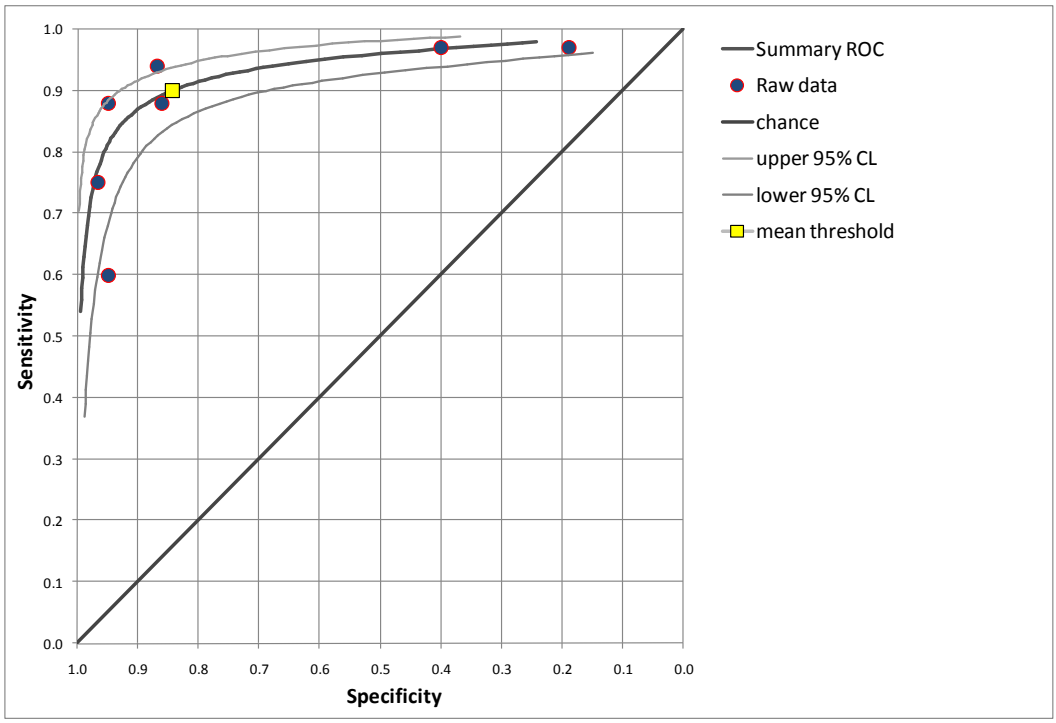
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 23. SROC-Level III Portable Systems (Threshold AHI ≥30)



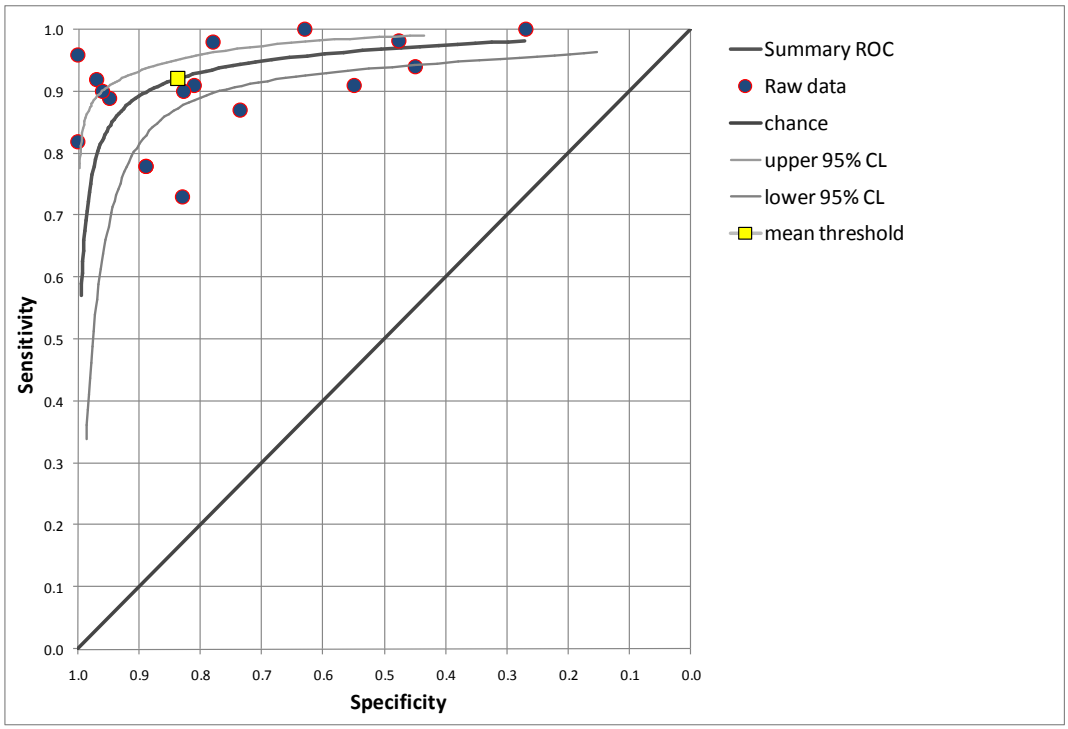
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 24. SROC-Level IV Portable Systems (Threshold AHI ≥5)



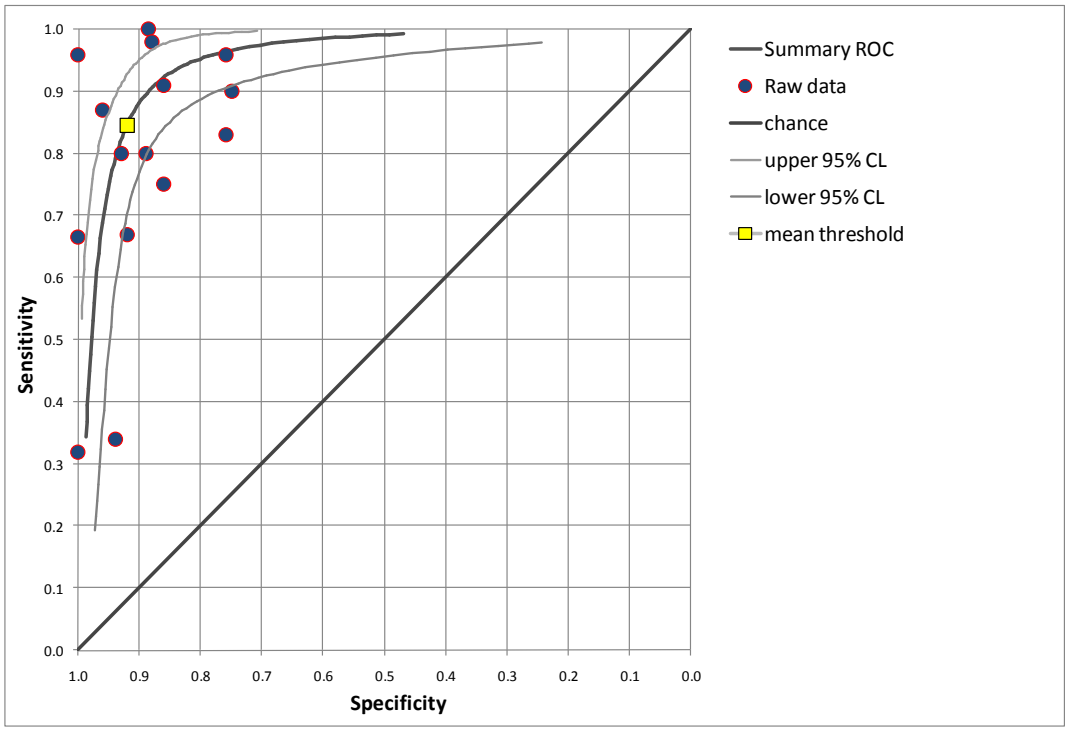
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 25. SROC-Level IV Portable Systems (Threshold AHI ≥10)



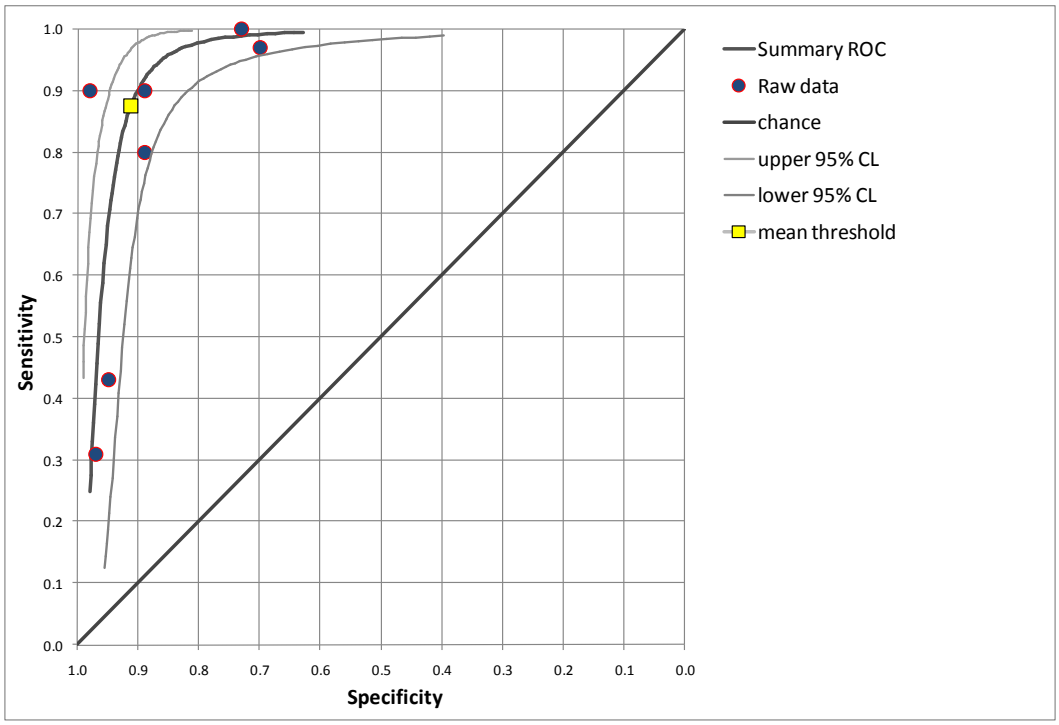
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 26. SROC-Level IV Portable Systems (Threshold AHI ≥15)



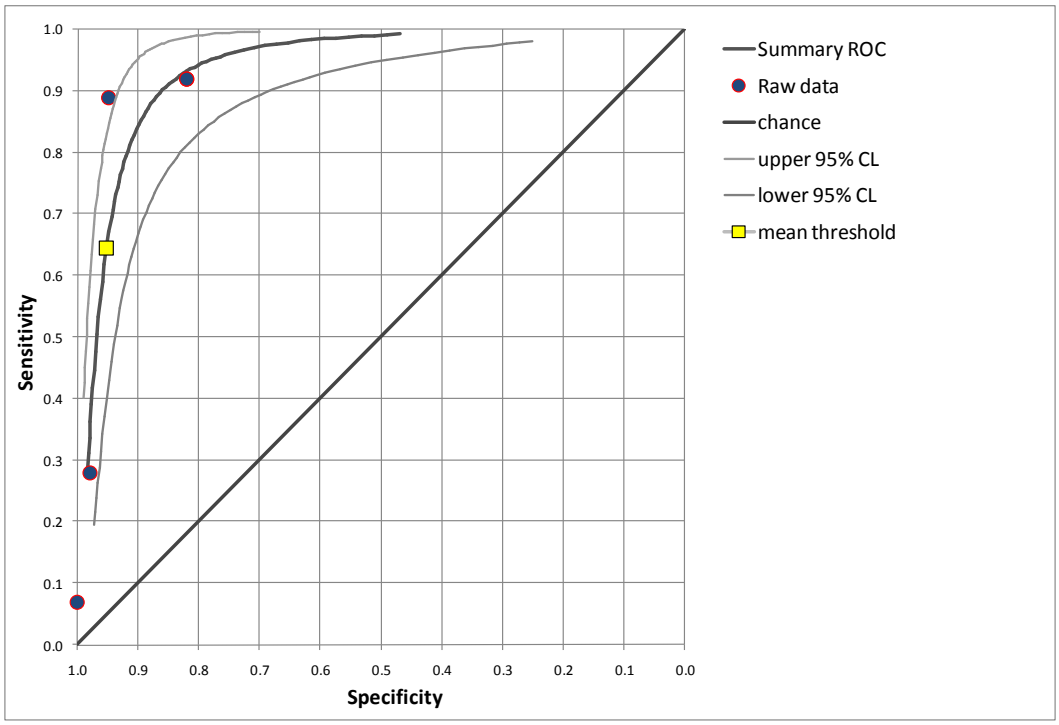
CL = Confidence level; ROC = Receiving operator characteristic.

Figure 27. SROC-Level IV Portable Systems (Threshold AHI ≥20)



CL = Confidence level; ROC = Receiving operator characteristic.

Figure 28. SROC-Level IV Portable Systems (Threshold AHI ≥30)



CL = Confidence level; ROC = Receiving operator characteristic.

Summary of Findings

The findings of our analyses of the data extracted from the 43 included studies that addressed Key Question 4 are as follows:

- **To date, no model or psychometric instrument has been shown to accurately stratify individuals with OSA by disease severity (a surrogate marker for crash risk).**
- **A number of portable sleep monitoring systems, though not as accurate as the current reference standard (a sleep study in a specialized sleep lab), do offer an alternative method by which the severity of OSA may be assessed in a large number of individuals at a relatively low cost.**
    - **It is not clear whether these systems are accurate enough to be considered as acceptable alternatives to the current reference standard for stratifying individuals by OSA severity for the purposes of making decisions about the fitness of an individual to drive a CMV. Addressing this issue will requires that a formal decision and cost-effectiveness analyses be performed. Such analyses are beyond the scope of this evidence report.**

To date, no RCT has been published that compares OSA-related outcomes known to be associated with driver safety among individuals with OSA who were stratified into risk groups using PSG or an alternative diagnostic test. Consequently, one must attempt to estimate the likely consequences of replacing standard PSG with cheaper, more easily accessible portable sleep monitoring systems using indirect methods. The first stage in this process is to obtain accurate estimates of the diagnostic performance characteristics of available systems. Once such estimates are identified, a decision model needs to be developed into which these diagnostic performance data can be integrated along with other necessary data (e.g., the costs associated with each diagnostic decision option, the prevalence of severe OSA in the U.S. CMV driver population).

While no portable sleep monitoring system was as accurate as the reference standard (none had a sensitivity and specificity of 100%), our analyses found that the diagnostic performance characteristics of most portable systems were reasonable. That is, the vast majority of available systems could differentiate individuals with OSA from those without, and they could differentiate individuals with severe OSA from those with mild-to-moderate disease better than would be expected by chance alone.

Although we have synthesized the diagnostic performance characteristics of Level II, Level III, and Level IV sleep monitors, we caution the reader that the precision of these estimates is low. While the quality of the included studies was moderate-to-high and the quantity of available evidence was reasonably large, a great deal of heterogeneity in the findings of different studies was observed, even when the tests were performed at the same threshold of OSA severity. Attempts to model this heterogeneity were unsuccessful, and none of the more obvious covariates, such as differences in the device used, the setting in which the study was performed (lab or at home), or the availability of a technician, appeared to be associated with diagnostic performance differences. Indeed, homogeneity testing of diagnostic performance data extracted from studies that used the same device at the same threshold were also found to be heterogeneous.

Whether currently available portable sleep monitoring systems are accurate enough to be considered as acceptable alternatives to the current reference standard for stratifying individuals by OSA severity for the purposes of making decisions about the fitness of an individual to drive a CMV is unclear. Addressing this issue requires that a formal decision and cost-effectiveness analyses be performed. Such analyses, though time consuming and expensive, are central to any decision or policy-making program and fall within the purview of FMCSA's Analysis Division.

Key Question 5: Which treatments have been shown to effectively reduce crash risk among individuals with OSA? Where reductions in crash risk have been assessed:

a) directly (crash risk)

b) quasi-directly (simulated driving performance)

c) indirectly (OSA severity, EDS, cognitive and psychomotor function, blood pressure, SaO_2)

Introduction

As demonstrated in Key Question 1, patients with moderate-to-severe OSA are at an increased risk for a motor vehicle crash. The purpose of this section of the Evidence Report is to assess the evidence pertaining to the impact of currently utilized treatments for OSA on driver safety. Basic descriptions of behavioral-, pharmacologic-, surgical-, and device-based treatments considered in this section of the Evidence Report are provided in the *Background* section.

For the sake of clarity, we have divided this section of the Evidence Report into three separate subsections. The first subsection examines evidence from studies that have directly addressed the question of whether currently utilized treatments for OSA can reduce the risk for a motor vehicle crash. The second and third subsections examine the evidence from studies that have indirectly examined the impact of available treatments for OSA on crash risk. Indirect measures assessed include simulated (or experimental[15]) driving performance and several factors that are known to be associated with an increased risk of a crash in individuals with OSA. These factors include severity of disease, level of daytime sleepiness, blood pressure, cognitive and psychomotor function, and SaO_2 levels.

Key Question 5: Part A - Effect of Available Treatments on Crash Risk

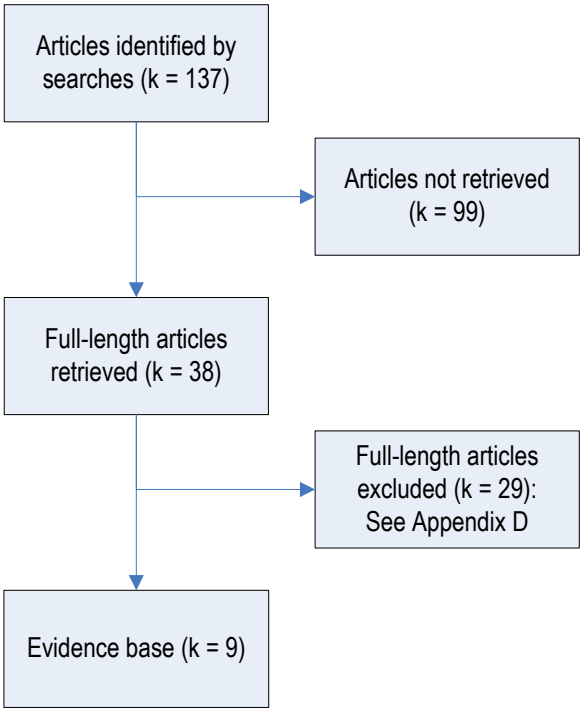
In this subsection we examine the available evidence pertaining to the influence of current OSA treatments on the increased risk for a motor vehicle crash that is associated with the disorder.

Identification of Evidence Base

The pathway by which the evidence base for Key Question 5: Part A was identified is summarized in Figure 29. Our searches (Appendix A) identified a total of 137 articles that appeared to be relevant to this key question. Following application of the retrieval criteria (Appendix B) for this question, 38 full-length articles were retrieved and read in full. Of these 38 retrieved articles, nine articles were found to meet the inclusion criteria (Appendix C) for Key Question 5: Part A. Table D-5 of Appendix D lists the 29 articles that were retrieved but not included in the evidence base for this question.

[15] Experimental driving performance refers to tests of driving performance carried out in a real vehicle on a special test track or circuit.

Figure 29. Development of Evidence Base for Key Question 5: Part A



Evidence Base

All nine studies that met the inclusion criteria for Key Question 5: Part A examined the impact of CPAP on crash risk; no other treatment option was studied (Table 41). Consequently, one is precluded from determining whether treatment options other than CPAP reduce the risk for a crash among individuals with OSA.

Table 41. Evidence Base: Studies of Impact of Available Treatments for OSA on Crash Risk

Reference	Year	Country	Behavioral Modification	CPAP	Dental Appliances	Medication	Surgery
Barbe et al.(68)	2006			✓			
George et al.(151)	2001			✓			
Findley et al.(72)	2000			✓			
Horstmann et al.(73)	2000			✓			
Scharf et al.(152)	1999			✓			
Yamamoto et al.(89)	1999			✓			
Krieger et al.(153)	1997			✓			
Cassel et al.(78)	1996			✓			
Engelman et al.(92)	1996			✓			
Total Number of Studies =			**0**	**9**	**0**	**0**	**0**

CPAP = Continuous positive airway pressure.

The primary characteristics of the nine included studies that address Key Question 5: Part A are presented in Table 42. To date, no prospective trial, either randomized or nonrandomized, has attempted to examine the treatment impact on crash rates among individuals with OSA. Given the long follow-up times that are required to obtain an adequate quantity of crash-rate data for meaningful analysis (as crash is a rare event), it seems unlikely that such a study will be performed in the future for ethical reasons. It is difficult to justify withholding treatment to an individual with moderate-to-severe OSA for a period of two or more years.

All nine included studies utilized a retrospective before-after study design in which individuals with moderate-to-severe OSA (as determined by PSG in a sleep lab), all of whom were candidates for treatment with CPAP, were queried about their motor vehicle crash history during some time period (from one to five years) preceding enrollment in the study. Following a corresponding period of time on treatment, patients were again asked about their crash history. The difference between the pretreatment crash rate and the post-treatment crash rate was calculated, and this outcome was assumed to be the consequence of treatment.

While for the purposes of addressing Key Question 5: Part A, all nine included studies must be considered as before-after studies, three studies did utilize a control group.(68,72,151) In all three cases, this control group was comprised of individuals who did not have OSA. Data from these individuals were used to determine whether the post-treatment crash risk was reduced to a rate that was similar to that

expected among comparable individuals without OSA. In all three cases, individuals in the control group were matched to those in the OSA group by age and sex. Only one of the studies attempted to match cases and controls for driving exposure.(151)

Different studies collected different types of crash data. Some studies included any motor vehicle crashes in their estimates; others only considered crashes which resulted in property damage. Still, others defined a crash as being any collision in which the individual of interest was deemed responsible. Between-studies differences in the type of crash data considered may manifest themselves as between-studies heterogeneity. This may impede our ability to provide an accurate estimate of the true effects of treatment on crash risk.

Table 42. Characteristics of Studies that Examined the Influence of CPAP on Crash Risk

Reference	Year	Study Design	Method of Diagnosis	Prospective?	Comparison of Interest	Number of Individuals Treated (n =)	Device Details	Was Compliance Assessed?	Factors Controlled for (If Compared to Nonapnic Controls)?	Exposure Controlled for (If Compared to Nonapnic Controls)?	Crash Data Objective?
Barbe et al.(68)	2006	Before-After + case-control*	PSG in sleep lab	No	Before vs. after treatment OSA group vs. healthy control	80			Age, sex, alcohol consumption	No	No
George et al.(151)	2001	Before-After + case-control*	PSG in sleep lab	No	Before vs. after treatment OSA group vs. healthy control	210	Nasal CPAP No other details	Yes self-report	Age, sex, driver class	Yes? Driver class	Yes (MTO data)
Findley et al.(72)	2000	Before-After + case-control*	PSG in sleep lab	No	Before vs. after treatment CPAP group vs. no CPAP group OSA group vs. healthy control	36	Nasal CPAP No other details	Yes self-report	Age, sex	No	Yes (State DMV records)
Horstmann et al.(73)	2000	Before-After	PSG in sleep lab	No	Before vs. after treatment	71	Nasal CPAP No other details	Yes self-report	NA	NA	No
Scharf et al.(152)	1999	Before-After	PSG in sleep lab		Before vs. after treatment	316	Nasal CPAP No other details	Yes self-report	NA	NA	No
Yamamoto et al.(89)	1999	Before-After	PSG in sleep lab	No	Before vs. after treatment	39	Nasal CPAP 7300H, France Bed Medical	Yes self-report	NA	NA	No
Krieger et al.(153)	1997	Before-After	Full PSG or on respiratory polygraphy in sleep lab	No	Before vs. after treatment	893	Nasal CPAP No other details	Yes self-report	NA	No	No
Cassel et al.(78)	1996	Before-After	PSG in sleep lab	No	Before vs. after treatment	78	Nasal CPAP No other details	Yes self-report	NA	NA	No
Engelman et al.(92)	1996	Before-After	PSG in sleep lab	No	Before vs. after treatment	253	Nasal CPAP No other details	Yes self-report	NA	NA	No

*For the purposes of the primary question, which asks whether CPAP reduces crash risk among individuals with OSA, the study is a before-after study. However, for the purposes of asking whether individuals treated with CPAP have a crash risk that is similar to that expected among individuals without the disorder, this study is a case-control study.

CPAP Continuous positive airway pressure; DMV Department of motor vehicles; MTO Ministry of Transportation of Ontario; NA Not applicable; OSA Obstructive sleep apnea; PSG Polysomnogram.

Quality of Studies that Examined Impact of Treatments for OSA on Crash Risk

Our assessment findings of the quality of the studies that comprise the evidence base for Key Question 5: Part A are presented in Table 43. Overall, our analysis found the quality of the studies in the evidence base to be low.

Table 43. Quality of Included Studies that Examined the Influence of CPAP on Crash Risk

Reference	Year	Quality-assessment Instrument Used	Quality Rating
Barbe et al.(68)	2006	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
George et al.(151)	2001	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Findley et al.(72)	2000	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Horstmann et al.(73)	2000	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Scharf et al.(152)	1999	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Yamamoto et al.(89)	1999	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Krieger et al.(153)	1997	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Cassel et al.(78)	1996	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low
Engelman et al.(92)	1996	ECRI Institute Quality Assessment Instrument: Before-After Studies	Low

As noted previously, all nine of the studies that examined the effects of CPAP on crash risk among individuals with OSA are, for the purposes of this key question, considered to be before-after studies. Before-after studies are susceptible to several sources of bias. A particularly worrisome potential source of bias arises from the fact that the time periods over which on- and off-treatment crash data are collected are not concurrent. Pretreatment crash data were collected retrospectively, and post-treatment crash data were, in general, collected prospectively following entry into the study. A problem with this data collection approach is that individuals who enter a study and are aware of its purpose will not behave in the same manner as they did prior to entering the study; a phenomenon known as the Hawthorne effect. In this case, individuals enrolled in the included studies may become more aware of their driving behavior and begin to drive more carefully, thus reducing the likelihood of a crash.

Along a similar vein, a design problem common to many risk assessment studies is the failure to control adequately for exposure. In this instance, the exposure variable of critical importance is the number of miles driven per unit time. Exposure cannot be controlled for in a before-after study. Consequently, it is important that articles describing such studies report on exposure to risk prior to the onset of treatment and also during the follow-up period following treatment. Such information was not presented by any included study. This limits the confidence that one can have in the causal relationship between treatment and any change in crash rate observed prior to and following the onset of that treatment.

The sample size of individuals enrolled in the included studies ranged from 36 to 893, and the observation periods over which pre-and post-treatment crash rates were determined ranged from 6 months to 5 years. Small studies with short observation periods may underestimate crash rates, because there is a high probability that a crash will not be observed. For example, neither Yamamoto et al.(89) nor Findley et al.(72) (the two smallest studies in the evidence base) observed any crashes among individuals enrolled in their study following treatment initiation. A crash rate of 0.0 crashes per person year is clearly not a realistic estimate of the crash rate among any group of individuals.

Crash rate data reported by seven of the included studies was based on self report.(68,73,78,89,92,152,153) The degree of confidence that one can have in crash rates obtained in this manner is unclear, primarily because questionnaires depend on the memory and honesty of the individual being questioned. The remaining two studies obtained crash data from a State or Provincial government agency.(72,151) Findley et al. obtained crash data from the Department of Motor Vehicles of the State of Colorado.(72) George et al. obtained crash data from the Ontario Ministry of Transportation.(151) Since we have no way of determining the accuracy of the information contained within these databases, the degree of confidence that one may have in data extracted from them is not clear.

Generalizability of Studies that have Assessed CPAP and Crash Risk

The characteristics of the individuals with OSA enrolled in the nine studies that comprise the evidence base for Key Question 5: Part A are summarized in Table 44. Enrolled individuals tended to be middle aged, obese males with moderate-to-severe sleep apnea. The generalizability of these individuals to CMV drivers is unclear, as none of the studies focused on the impact of CPAP on crash risk among CMV drivers with OSA. Four of the nine studies reported on the amount of driving to which their enrollees were exposed. All four studies reported annual mileage figures that are far lower than those associated with professional drivers. None of these four studies reported on the type of driving (highway, local driving only, night driving, etc.) engaged in by enrollees. The remaining five included studies did not provide any driving exposure information at all.

Table 44. Characteristics of Individuals with OSA Enrolled in Studies that Examined the Influence of CPAP on Crash Risk*

Reference	Year	Mean Age (SD)	AHI (SD)	Mean BMI (SD)	Mean ESS (SD)	Sleeping Hours/Day	% male	Driving Exposure	% CMV Drivers	Generalizability to CMV Drivers
Barbe et al.(68)	2006	49 years (SEM: 1)	>20 per hour	33 kg/m^2 (SEM: 0.7)	12 (SEM: 1.0)	8.4 (SEM: 0.2)	97.5	25,000 km/year (SEM: 2,000)	NR	Unclear
George et al.(151)	2001	51 years (11)	54 per hour (29)	35.5 kg/m^2 (10)	NR	NR	NR	22,700 km/year (16,500)	NR	Unclear
Findley et al.(72)	2000	54 years (SEM: 2)	37.9 per hour (SEM: 5.0)	NR	NR	NR	83.3	NR	NR	Unclear
Horstmann et al.(73)	2000	NR	NR	NR	NR	NR	NR	17,784 km/year	NR	Unclear
Scharf et al.(152)	1999	48.8 years (SEM: 0.7)	42.9 per hour (SEM: 1.7)	NR	NR	NR	74.1	NR	NR	Unclear
Yamamoto et al.(89)	1999	49.5 years (10.8)		29.2 kg/m^2 (5.4)	12.6 (4.9)	NR	100.0	NR	NR	Unclear
Krieger et al.(153)	1997	56.6 years (10.7)	34.9 per hour (21.1)	33.7 kg/m^2 (6.8)	NR	5.58 (1.4)	86.5	NR	NR	Unclear
Cassel et al.(78)	1996	48.0 years (SEM:1.0)	34.2 per hour (SEM: 3.1)	31 kg/m^2 (SEM: 0.6)	NR	6.1 (SEM: 0.16)	100.0	29,606 km/year (SEM: 2,367)	NR	Unclear
Engelman et al.(92)	1996	46 years (9)	47 (38)	NR	15.6 (6.0)	5.8 (2.0)	NR	NR	NR	Unclear

*This table provides details of the characteristics of individuals who were treated with CPAP.

AHI = Apnea-hypopnea index; BMI Body mass index; CMV Commercial motor vehicle; ESS Epworth sleepiness scale; NR Not reported; SD Standard deviation; SEM Standard error of measurement.

Findings of Studies that have Assessed Influence of Available Treatments for OSA on Crash Risk

Nine included studies (Median Quality Rating: Low) presented data on the effect of CPAP on crash risk among individuals with moderate-to-severe OSA. The findings of these studies are presented in Table 45. With one exception, reductions in crash risk while on CPAP from baseline levels were substantial (Figure 30). The exception to this finding was for the subgroup of individuals in the study of Engelman et al. who experienced noninjurious crashes and appeared to gain no benefit from CPAP. Why the findings from this group of individuals differs so markedly from the remainder of the findings reported in this section is not clear. Because this subgroup of individuals included in Engelman et al. is an outlier, we have not included it in the remainder of our analyses.

Tests of the remaining data from the nine included studies for homogeneity found that these data were heterogeneous ($Q = 62.56$, $p<0.001$; $I^2 = 87.22$). Consequently, we did not pool these data using a fixed-effects meta-analysis, nor did we attempt to explore this heterogeneity using meta-regression[16].

Pooling of the data using a random-effects model meta-analysis (Figure 32) found that CPAP significantly reduces the risk for a motor vehicle crash among individuals with severe OSA (Pre-Post Treatment Crash RR = 0.278, 95% CI: 0.22 to 0.35; $p<0.001$). This reduction in crash risk following the onset of treatment, which is in the order of 65% to 78%, represents a substantial decrease in the excess crash risk associated with OSA. A series of sensitivity analyses (Appendix H) found the findings of this analysis to be robust.

To determine whether excluding data from the subgroup of individuals included in Engelman et al. who experienced noninjurious crashes from the analysis above had an impact on our findings, we performed an additional sensitivity analysis. In this analysis, we examined the impact of replacing the findings from the injurious treatment group of Engelman et al. with crash data from the group of individuals who experienced noninjurious crashes. This analysis confirmed the robustness of our original findings.

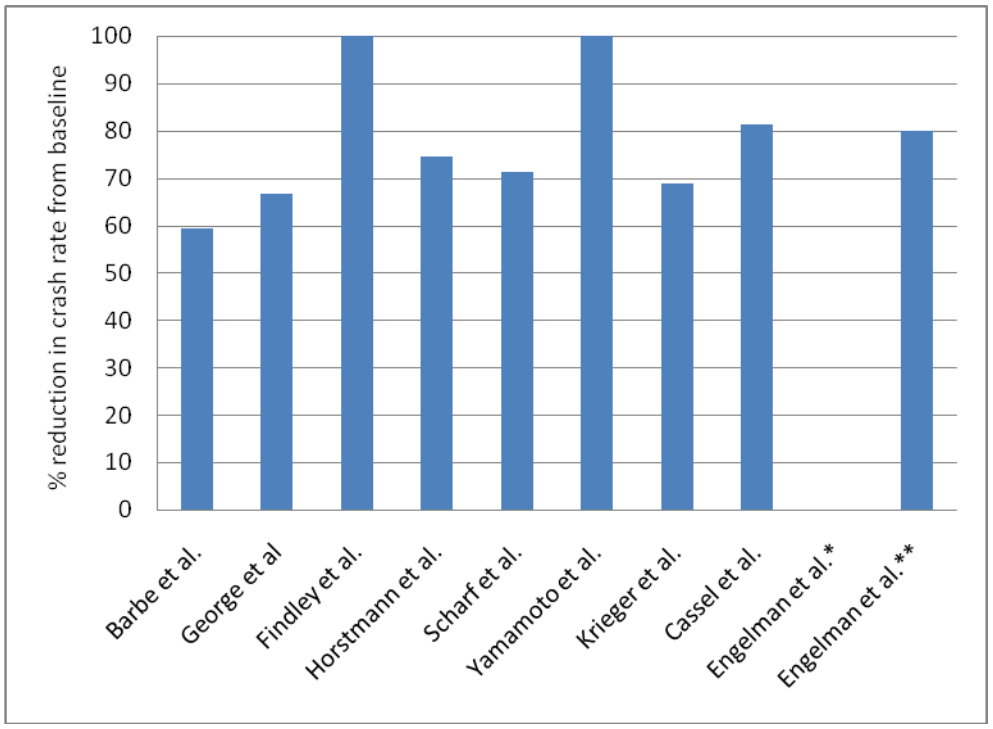
[16] The ECRI Institute requires relevant data from at least 10 studies in order for meta-regression or subgroup analysis to be attempted.

Table 45. Crash Rate Prior to and Following Treatment with CPAP

Reference	Year	Definition of Crash	Crash Rate Prior to Treatment	Observation Period	Crash Rate After Treatment	Observation Period	Crash Rate Reduction (95% CI)	% Reduction in Risk	Crash Rate Ratio (95% CI)	p-value
Barbe et al.(68)	2006	Crash with property damage	9.20 per 1,000,000 km	2 years	3.74 per 1,000,000 km	2 years	5.46 (NC) per 1,000,000	59.3	0.40 (0.37 to 0.45)	<0.001
George et al.(151)	2001	Any motor vehicle crash	0.18 (SD: 0.29) per person/year	3 years	0.06 per (SD:0.17) person/year	3 years	0.12 (0.06 to 0.17) per person/year	66.7	0.33 (0.23 to 0.48)	<0.001
Findley et al.(72)	2000	At-fault crash with property damage and conviction for violation	0.07 per person/year	2 years	0.00 per person/year	2 years	0.07 (NC) per person/year	100.0	0.09 (0.00 to 1.63)	0.103
Horstmann et al.(73)	2000	Any crash while driving	10.60 per 1,000,000 km	3 years	2.70 per 1,000,000 km	Mean of 15.4 months	7.9 (NC) per 1,000,000 km	74.5	0.26 (0.23 to 0.28)	<0.001
Scharf et al.(152)	1999	Any motor vehicle crash or “near miss”	6.08 per person/year	6 months	1.74 per person/year	6 months	4.34 (NC) per person/year	71.4	0.29 (0.25 to 0.33)	<0.001
Yamamoto et al.(89)	1999	Any motor vehicle crash	0.16 per person/year	2 years	0.00 per person/year	2 years	0.16 (NC) per person/year	100.0	0.04 (0.00 to 0.65)	0.024
Krieger et al.(153)	1997	Any motor vehicle crash	0.08 per person/year	1 year	0.025 per person/year	1 year	0.055 (NC) per person/year	68.8	0.31 (0.19 to 0.50)	<0.001
Cassel et al.(78)	1996	Any crash while driving	0.80 per 100,000 km	5 years	0.15 per 100,000 km	1 year	0.65 (NC) per 100,000 km	81.3	0.19 (0.13 to 0.27)	<0.001
Engelman et al.(92)	1996	Any noninjurious crash	0.09 (0.44) per 10,000 miles	5 years	0.09 (0.52) per 10,000 miles	16 to 2,921 days	0.00	0.0	1.00 (0.75 to 1.34)	1.00
		Any injurious crash	0.005 (0.027) per 10,000 miles	5 years	0.001 (0.015) per 10,000 miles	16 to 2,921 days	0.004	80.0	0.20 (0.10 to 0.39)	<0.001

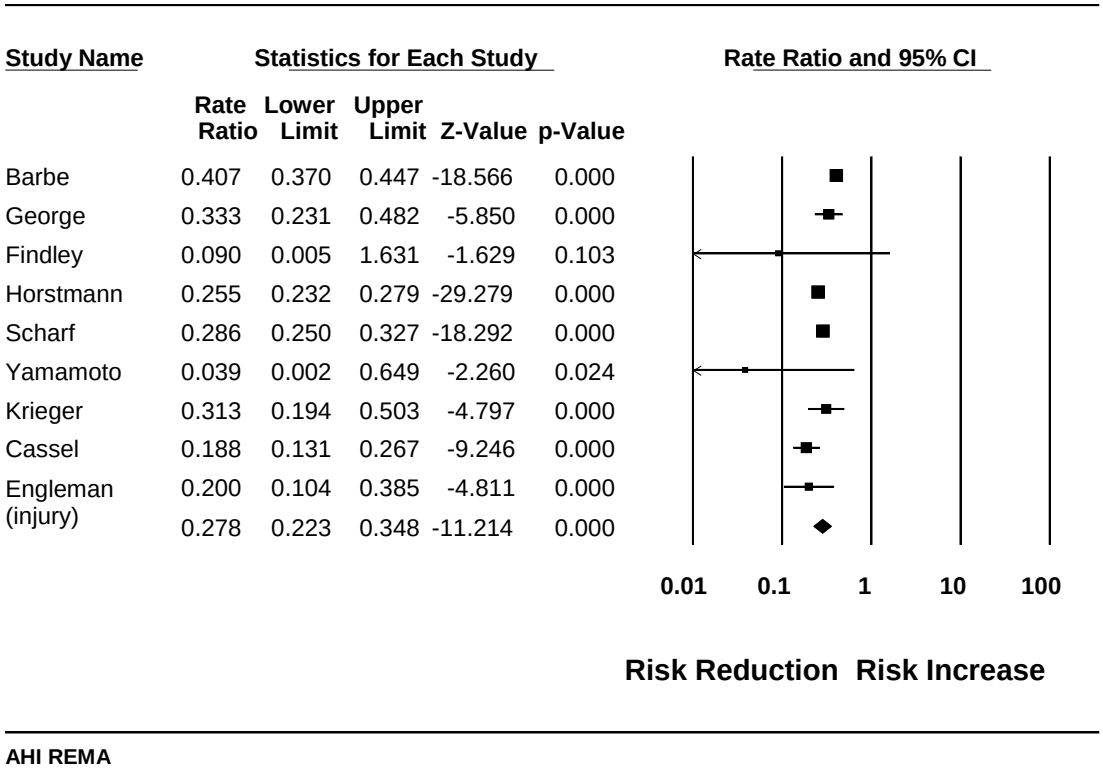
NC = Not calculated.
SD = Standard deviation.

Figure 30. % Reduction in Crash Rate Following Treatment with CPAP



* Any noninjurious crash
** Any injurious crash

Figure 31. Random-effects Meta-analysis of Pre-post CPAP Crash Risk Ratio Data



Although the findings of the above studies demonstrate that CPAP treatment reduces the risk of experiencing a motor vehicle crash among drivers with severe OSA, it remains unclear whether the observed reductions in crash risk are large enough to reduce crash risk among this population to the extent expected among comparable individuals without the disorder. In order to determine this, we examined data from the three included studies that directly compared post-treatment crash rates from OSA patients with a control group comprised of comparable individuals without the disorder.(68,72,151) The findings of these studies are summarized in Table 46.

Table 46. Does CPAP Treatment Eliminate Excess Crash Risk in Individuals with OSA

Reference	Year	Crash Rate After Treatment	Time Period	Non-OSA Control Crash Rate	Time Period	Crash Rate Ratio (95% CI)	p-value
Barbe et al.(68)	2006	3.74 per 1,000,000 km	2 years	1.74 per 1,000,000 km	2 years	2.15 (1.87 to 2.48)	<0.001
George et al.(151)	2001	0.06 crashes per person/year	3 years	0.07 crashes per person/year	3 years	0.86 (0.56 to 1.32)	0.487
Findley et al.(72)	2000	0.00 crashes per person/year	2 years	0.01 crashes per person/year	2 years	0.41 (0.02 to 11.01)	0.595

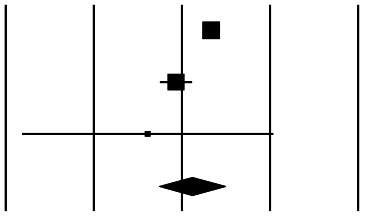
OSA = Obstructive sleep apnea.

The findings of the three studies included in Table 46 are inconsistent. One included study found that, despite large reductions in crash risk, individuals treated with CPAP remain at an increased risk for a motor vehicle crash.(68) The remaining two studies, however, found no evidence that CPAP-treated individuals remain at an increased risk for a motor vehicle crash.(72,151) Formal heterogeneity testing confirmed that the findings of the three studies were inconsistent ($q = 16.41$, $p < 0.001$; $I^2 = 87.81$). Because the size of the evidence precludes exploration of this heterogeneity, one is precluded from using meta-regression to determine the reason that the findings of Barbe et al. differ so markedly from those of George et al. and Findley et al.

Pooling of these data using a random-effects meta-analysis (Figure 32) found that, despite treatment with CPAP, individuals with OSA demonstrate a tendency for experiencing more crashes than their counterparts who do not have the disorder (RR = 1.29, 95% CI: 0.55 to 3.06). Because the confidence intervals encompass an RR of one (1), however, one cannot discern whether this tendency in the data is meaningful. We thus refrain from drawing an evidence-based conclusion pertaining to whether CPAP reduces crash risk to that experienced by individuals who do not have OSA at this time.

Figure 32. Random-effects Meta-analysis of Post CPAP Crash Risk versus No OSA Controls

Study Name	Rate Ratio	Lower Limit	Upper Limit	Z-Value	p-Value
Barbe	2.149	1.865	2.478	10.548	0.000
George	0.857	0.555	1.324	-0.695	0.487
Findley	0.410	0.015	11.014	-0.531	0.595
	1.292	0.546	3.058	0.583	0.560



AHI REMA

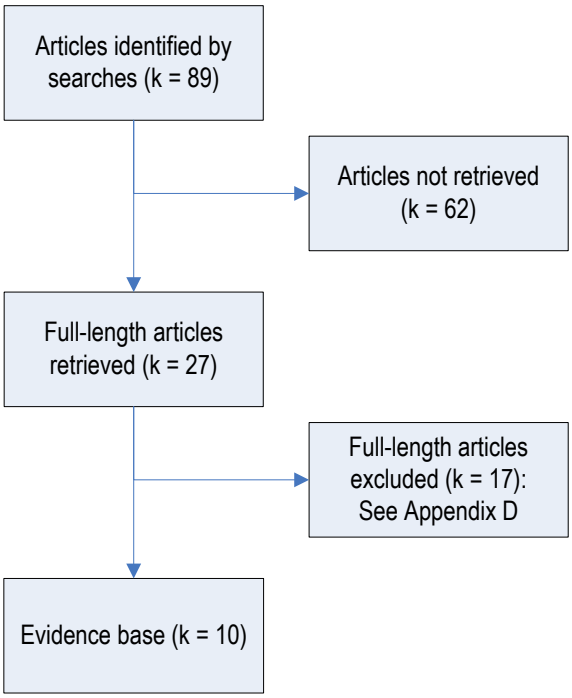
Key Question 5: Part B - Effect of Available Treatments on Simulated Driving Performance

In this subsection we examine the available evidence pertaining to the influence of available treatments for OSA on simulated driving performance. Several studies have demonstrated that driving performance is reduced among untreated individuals with moderate-to-severe OSA when compared to similar individuals who do not have the disorder.(154-157) The purpose of this section is to determine whether available treatments for OSA improve driving performance in this group of individuals to a level that can be considered normal.

Identification of Evidence Base

The process by which the evidence base for Key Question 5: Part B was identified is summarized in Figure 33. Our searches (Appendix A) identified a total of 89 articles that appeared to be relevant to this key question. Following application of the retrieval criteria (Appendix B) for this question, 27 full-length articles were retrieved and read in full. Of these 27 retrieved articles, 10 articles were found to meet the inclusion criteria (Appendix C) for this key question. Table D-5 of Appendix D lists the 17 articles that were retrieved but then excluded from inclusion in the evidence base.

Figure 33. Development of Evidence Base for Key Question 5: Part B



Evidence Base for Key Question 5: Part B

The treatments for OSA that were assessed by the studies that comprise the evidence base for Key Question 5: Part B are presented in Table 47. Eight studies assessed the impact of CPAP on simulated driving performance. The impact of dental appliances, medication, and surgery, respectively, were each assessed by one study (Hoekema et al. evaluated CPAP and dental appliances in their study). No included study assessed the impact of behavioral modification on simulated driving performance.

Table 47. Treatments Considered by Included Studies

Reference	Year	Country	Behavioral Modification	CPAP	Dental Appliances	Medication	Surgery
Mazza et al.(154)	2006	France		✓			
Hoekema et al.(155)	2006	Netherlands		✓	✓		
Orth et al.(158)	2005	Germany		✓			
Turkington et al.(159)	2004	UK		✓			
Buttner et al.(160)	2003	Germany				✓	
Hack et al.(161)	2001	UK		✓			
Hack et al.(162)	2000	UK		✓			
George et al.(156)	1997	Canada		✓			
Haraldsson et al.(163)	1995	Sweden					✓
Findley et al.(157)	1989	USA		✓			
		Totals =	**0**	**8**	**1**	**1**	**1**

CPAP = Continuous positive airway pressure.

Attributes of Studies that have Assessed Effects of OSA Treatments on Driving Simulator Performance

Important characteristics of the 10 included studies that address Key Question 5: Part B are presented in Table 48. A more comprehensive description of each of these studies can be found in the relevant Study Summary Tables found in Appendix G.

Simulated driving performance was assessed in two ways: using a real vehicle on an experimental test track or on a simulator. Most studies utilized one of these mechanisms; however, both methods were used in one study.(154)

Mazza et al. tested driving performance using a "road safety test platform" called Minotaure and a CRT-based driving simulator. This platform is made up of two separate one-way tracks (one in each direction) that are approximately 150 meters long and 3 meters wide. The platform is fitted with digital cameras and magnetic detectors that enable recording of several parameters during an emergency braking task. Once a test vehicle hits the track at the required speed, a jet of water is released that forms an "obstacle." The production and position of the water jet are calculated according to the vehicle's speed and its position on the track. They are calculated this way in order to appear at an average distance of 40 meters in front of the vehicle, without the subject being able to anticipate its occurrence and its location. As soon as the obstacle is visible, the subject is required to stop his/her vehicle as quickly as possible in order to avoid impact.

Table 48. Design Characteristics of Included Studies

Reference	Year	Study Design	Method of Diagnosis	Prospective ?	Comparison	Period data collected?	Number treated?	Number in Control Group	Items Individuals Matched for	Simulator or Test Track	Driving Exposure controlled for?
Mazza et al.(154)	2006	Controlled Trial	PSG	Prospective	CPAP versus normal controls	3 months	20	20	Age, educational	Minotaure (test track) CRT-based simulator	Yes, # of years driving (15 minimum) and current exposure
Hoekema et al.(155)	2006	RCT	PSG	Prospective	CPAP Oral Appliances	3 months	20	16	Age	Driving simulation machine in the Dept. of Neuropsychology at the University of Groningen, The Netherlands	NR
Orth et al.(158)	2005	Case Series	PSG	Prospective	CPAP	42 days	31	NA	NA	C.A.R.	NA
Turkington et al.(159)	2004	Controlled Trial	Recruited from a sleep clinic	Prospective	CPAP versus no treatment	21 days	18	18	Age, gender	SIMDrive Divided Attention Driving Simulator (DADS)	NR
Buttner et al.(160)	2003	RCT – with cross-over	PSG	Prospective	Theophylline versus placebo	2 days	39	NA	NA	CarSim	NA
Hack et al.(161)	2001	Controlled Trial	PSG	Prospective	CPAP vs. controls on either alcohol or sleep deprivation	28 days	26	NA	NA	Steering Simulation Test plus Divided Attention Task	NA
Hack et al.(162)	2000	RCT	PSG	Prospective	CPAP versus sham (subtherapeutic) CPAP	1 month	26	33	Age, gender	Steering Simulator Test based on Land's research	Yes, similar years experience
George et al.(156)	1997	Controlled Trial	Recruited from a previous OSA study	Prospective	CPAP versus normal controls	12 months	21	18	Age, gender	Divided Attention Driving Task (DADT)	Yes, similar years and current exposure
Haraldsson et al.(163)	1995	Controlled Trial	PSG	Prospective	UPPP versus normal controls	4 years	13	5	Age	Driving Simulator developed by the Swedish Road and Traffic Research Institute	Yes, similar experience
Findley et al.(157)	1989	Controlled Trial	Recruited at a university health center	Prospective	CPAP vs. normal controls	3 – 5 months	6	NA	NA	Doron Driving Simulator and an unspecified personal computer simulator test.	NA

*This was a controlled trial that compared OSA patients with comparable individuals without the disorder pre- and post-treatment – no comparison with a control group of individuals with OSA - for our purposes this is a before-after study

CAR = Computer-aided risk simulator; CPAP = Continuous positive airway pressure; CRT = Cathode-Ray Tube; DADS = Divided attention driving simulator; DADT = Divided attention driving task; NA = Not applicable; NR = Not reported; OSA = Obstructive sleep apnea; PSG = Polysomnogram; RCT = Randomized controlled trial; UPPP = Uvulopalatopharyngoplasty.

Quality of Studies that have Assessed CPAP and Driving Simulator Performance

The findings of our assessment of the quality of the studies that comprise the evidence base for Key Question 5: Part B are presented in Table 49. Overall, our analysis found the quality of the studies in the evidence base to be moderate-to-high.

Table 49. Quality of Included Studies

Reference	Year	Quality assessment Instrument Used	Quality Rating
Mazza et al.(154)	2006	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	High
Hoekema et al.(155)	2006	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	High
Orth et al.(158)	2005	ECRI Institute's Quality Item Checklist for Before-After Studies	Moderate
Turkington et al.(159)	2004	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	Moderate
Buttner et al.(160)	2003	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups with Crossover Questions	High
Hack et al.(161)	2001	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	Moderate
Hack et al.(162)	2000	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	High
George et al.(156)	1997	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	Moderate
Haraldsson et al.(163)	1995	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	Moderate
Findley et al.(157)	1989	ECRI Institute's Assessment Tool for Controlled Interventional Studies That Have Independent Groups	Moderate
Overall Quality			**Moderate**

Generalizability of Studies that have Assessed CPAP and Driving Simulator Performance

The generalizability of the findings of the included studies to CMV drivers is unclear. Not surprisingly, none of the included studies examined crash risk among individuals who held a current commercial driver's license. Exposure to risk is far lower among noncommercial vehicle drivers. This limits the value of the available data. It is worth noting, however, that the populations of the included studies were >50% male, and the age range was approximately 20 to 70 years. These factors may serve to make the study populations and the CMV driver population more similar and aid somewhat in generalizability of the information in this report.

Table 50. Characteristics of Individuals Enrolled in Included Studies

Reference	Year	Duration of Disease	Age distribution (years) mean±SD	BMI (Kg/m²)	% Male	Ethnicity	Driving Exposure	% CMV Drivers	Generalizability to Target Group
Mazza et al.(154)	2006	NR	CPAP Group: 54.1 ±5.9 years Control Group: 52.2 ±8.3 years	CPAP Group: 28.9 ±4.9 kg Control Group: 24.3 ±2.7 kg	CPAP Group: 90% Control Group: 85%	French	NR	NR	Unclear
Hoekema et al.(155)	2006	NR	OSA Group: 48.7 ±11.2 years Control Group: 48.7 ±10.0 years	OSA Group: 33.2 ±5.7 kg Control Group: NR	OSA Group: 85% Control Group: 82%	Dutch	OSA Group: 29 ±10 years Control Group: 29 ±11 years	NR	Unclear
Orth et al.(158)	2005	NR	Study Group: 55.3 ±10.2 years	Study Group: 29.9 ±2.2 kg	100%	German	NR	NR	Unclear
Turkington et al.(159)	2004	NR	CPAP Group: 49.9 ±10 years Control Group: 51.7 ±12.2 years	CPAP Group: 39 ±7.7 kg Control Group: 36.6 ±5.3 kg	94% both Groups	British	NR	NR	Unclear
Buttner et al.(160)	2003	NR	Study Group: 47.7 ±7.1 years	29.7 ±6.2 kg	100%	German	NR	NR	Unclear
Hack et al.(161)	2001	NR	Study Group: Median 50 years	32.2 kg	NR	British	31.5 years median	NR	Unclear
Hack et al.(162)	2000	NR	CPAP Group: Median 50 years Subtherapeutic CPAP: Median 50 years	CPAP Group: 32.2 kg Subtherapeutic CPAP: 34.0 kg	100%	British	CPAP Group: Median 31.5 years Subtherapeutic CPAP: Median 29.5 years	NR	Unclear
George et al.(156)	1997	NR	CPAP Group: 49.7 ±11.2 years Control Group: NR	NR	100%	NR	NR	NR	Unclear
Haraldsson et al.(163)	1995	NR	UPPP: Median 52 years Normal controls: Median 50 years	NR	100%	Swedish	NR	NR	Unclear
Findley et al.(157)	1989	NR	CPAP Group: 53 ±11 years Control Group: 50 ±14 years	NR	74%	NR	NR	NR	Unclear

BMI = Body mass index; CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; NR = Not reported; OSA Obstructive sleep apnea; SD = Standard deviation; UPPP = Uvulopalatopharyngoplasty.

Findings of Included Studies that Assessed Impact of Available Treatments for OSA on Simulated Driving Performance

The findings of each of the 10 included studies that address Key Question 5: Part B are summarized in Table 51. A complete report of the findings of each of these studies can be found within the Evidence Summaries that comprise Appendix G.

Table 51. Effect of Available Treatments for OSA on Driving Simulator Performance

Reference	Year	Measures	Baseline			Post Treatment				Evidence treatment improves driving perf.?
			Treatment Group Mean (SD)	Control Group Mean (SD)	Between Groups Differences	Treatment Group Mean (SD)	Control Group Mean (SD)	Within Groups Differences*	Between Groups Differences	
CPAP										
Mazza et al.(154)	2006	*Simple condition* • Reaction time (seconds) • Stopping distance (m) • Number of collisions n *Distraction condition* • Reaction time (seconds) • Stopping distance (m) • Number of collisions (n) • Actions *Anticipation condition* • Reaction time • Stopping distance • Number of collisions *Simulator – CRT-based* • Duration (seconds) • Divided attention • Off road events	Pre-CPAP 1.51 (0.35) 36.6 (10.7) 0.9 (0.7) 1.77 (0.34) 38.65 (6.0) 0.8 (0.7) 1.1 (0.8) 1.52 (0.45) 42.5 (7.0) 0.7 (0.9) 794.1 (439.4) 3.98 (2.47) 89.5 (116.7)	Normal controls 0.91 (0.21) 27.9 (6.5) 0.4 (0.5) 1.24 (0.48) 37.4 (4.5) 0.7 (0. 7) 1.6 (0.5) 1.17 (0.42) 38.9 (3.6) 0.2 (0.4) 1186.1 (62.2) 1.95 (0.87) 10.00 (12.5)	 p<0.001 p = 0.001 p = NS p<0.001 p = NS p = NS p = NS p = 0.02 p = 0.01 p = NS p<0.001 p<0.001 p<0.001	Post-CPAP 0.99 (0.22)* 28.4 (7.3) 0.1 (0.3)* 1.14 (0.32)* 31.6 (3.2)* 0.4 (0.7) 1.2 (0.6) 1.06 (0.34)* 33.7 (6.8)* 0.2 (0.4) 1080.6 (337.8)* 2.72 (0.78)* 27.6 (52.5)*	Normal controls 1.06 (0.13)* 27.8 (13.0) 0.2 (0.4) 1.22 (0.31) 34.0 (3.6) 0.3 (0.5) 1.7 (0.5) 1.13 (0.34) 37.3 (5.4) 0.4 (0.5) 1200.0 (0.0) 1.82 (0.50) 14.3 (17.7)	 p<0.05 p = NS p<0.05 p<0.05 p<0.05 p = NS p = NS p<0.05 p<0.05 p = NS p<0.05 p<0.05 p<0.05	 p = NS p = NS p = NS p = NS p = NS p = NS p = NS p = NS p = NS p = NS p = NS p<0.01 p = NS	YES (driving perf. Similar to normal controls)
Hoekema et al.(155)	2006	*Lapses of Attention* • Total (0-25 minutes) • First Epoch (0-5 minutes) • Second Epoch (6-10 minutes) • Third Epoch (11-15 minutes) • Fourth Epoch (16-20 minutes) • Fifth Epoch (21-25 minutes) • Slope coefficient of time course	Pre-CPAP 10.0 (IQR: 1.0-16.8) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-2.5) (IQR: 0.8-7.8) (IQR: 0.0-8.5) 0.63 (IQR: 0.04-0.90)	Normal control 0.0 (IQR: 0.0-1.8) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.03 (IQR: -0.15-0.17)	p>0.001† p = NS† p = 0.021† p = 0.005† p = 0.001† p<0.001† p = 0.006†	Post-CPAP 0.5 (IQR: 0.0-5.3) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.3) 0.0 (IQR: 0.0-1.0) 0.0 (IQR: 0.0-0.5) 0.0 (IQR: 0.0-2.5) 0.14 (IQR: -0.22-0.28)	Normal control NR	p = 0.03 p = NS p = NS p = NS p = 0.04 p = NS p = NS	NA	YES
Orth et al.(158)	2005	Crashes Concentration faults	Pre-CPAP 2.7 (2.0) 12.4 (5.1)	NA	NA	Pre-CPAP 0.9 (1.3) 4.9 (3.3)	NA	p<0.001 p<0.001	NA	YES
Turkington et al.(159)	2004	Tracking errors Reaction time Off-road events	Pre-CPAP 0.25 (NR) 2.10 (NR) 9	Untreated OSA 0.29 (NR) 2.60 (NR) 10	 p = NS p = NS p = NS	Post-CPAP 0.15 (NR) 1.40 (NR) 0	Untreated OSA 0.35 (NR) 2.60 (NR) 8	 NR NR NR	 p = 0.004 p = 0.036 p = 0.032	YES

Reference	Year	Measures	Baseline			Post Treatment				Evidence treatment improves driving perf.?
			Treatment Group Mean (SD)	Control Group Mean (SD)	Between Groups Differences	Treatment Group Mean (SD)	Control Group Mean (SD)	Within Groups Differences*	Between Groups Differences	
Hack et al.(161)	2001	Steering Error (SD) Off-road events (events/hour) Drive length (minutes) Reaction time (seconds)	Pre-CPAP 0.36 (95% CI: 0.15-1.10) 17.8 (95% CI: 0.35-248) 24.8 (95% CI: 5.36-30.0) 2.58 (95% CI: 1.75-4.80)	NA	NR NR NR NR	Post-CPAP 0.21 (95% CI: 0.15-0.72) 10.1 (95% CI: 0.17-75.7) 30.0 (95% CI: 17.5-30.0) 2.19 (95% CI: 1.47-3.55)	NA	p = 0.002 p = 0.004 p = 0.023 p<0.001	NA	YES
Hack et al.(162)	2000	SD of position on road SD deterioration (SD/hour) Off-road events (events/hour) Drive length (minutes) Reaction time (seconds)	Pre-CPAP (therapeutic) 0.36 (95% CI: 0.15-1.12) 0.18 (95% CI: -1.14-30.3) 17.8 (95% CI: 0.4-149) 24.9 (95% CI: 7.6-30.8) 2.8 (95% CI: 1.8-4.9)	Pre-CPAP (sham) 0.35 (95% CI: 0.15-1.17) 0.18 (95% CI: -0.12-2.67) 34.8 (95% CI: 0.90-149) 27.6 (95% CI: 11.2-20.8) 2.8 (95% CI: 1.7-5.5)	p = NS p = NS p = NS p = NS p = NS	Post-CPAP (therapeutic) 0.21 (95% CI: 0.14-0.63) 0.06 (95% CI: -1.02-0.40) 9.0 (95% CI: 0.0-76) 30.0 (95% CI: 17.6-30.0) 2.3 (95% CI: 1.5-3.5)	Post-CPAP (sham) 0.30 (95% CI: 0.14-1.19) 0.24 (95% CI: -0.14-2.64) 23.0 (95% CI: 0-150) 26.9 (95% CI: 9.1-30.0) 2.7 (95% CI: 1.6-4.0)	p = 0.001 p = 0.05 p = 0.004 p = 0.03 p<0.001	p = 0.08 p = 0.007 p = 0.07 p = 0.08 p = 0.04	YES
George et al.(156)	1997	Tracking error (cm) Response time (seconds) Correct responses (n) Missed responses (n) Out of bounds (n)	Pre-CPAP 228 (17.2) 3.2 (0.1) 36.2 (0.5) 3.7 (0.5) 12.6 (2.1	Normal Controls 82 (4.8) 2.6 (0.1) 39.3 (0.1) 0.6 (0.1) 0.1 (0.1)	p<0.001 p<0.001 p<0.001 p<0.001 p<0.001	Post-CPAP 113 (9.5) 2.8 (0.1) 37.8 (0.5) 2.2 (0.5) 2.6 (1.2)	Normal Controls 88 (6.9) 2.3 (0.1) 39.7 (0.1) 0.4 (0.1) 0.1 (0.1)	p<0.05 p<0.05 p<NS p<0.05 p<0.05	p = 0.032 p<0.001 p<0.001 p<0.001 p = 0.033	YES (still significantly worse than normal)
Findley et al.(157)	1989	Obstacles hit in 30 minutes	Pre-CPAP 29 (19)	Normal Controls 9 (7)	p<0.05	Post-CPAP 13 (8)	Normal Controls NR (NR)	p<0.05	NA	YES
Medication – Theophylline										
Buttner et al.(160)	2003	Tracking Deviation	NR	NR	NA	Post-Theophylline 13.6 (18.0)	Post-Placebo 49.3 (99.5)	NA	p = 0.025	YES
Oral Appliances										
Hoekema et al.(155)	2006	*Lapses of Attention* • Total (0-25 minutes) • First Epoch (0-5 minutes) • Second epoch (6-10 minutes) • Third Epoch (11-15 minutes) • Fourth Epoch (16-20 minutes) • Fifth Epoch (21-25 minutes) • Slope coefficient. Of time course	Pre-Appliance 5.0 (IQR: 2.0-14.0) 0.0 (IQR: 0.0-1.0) 0.0 (IQR: 0.0-1.0) 0.0 (IQR: 0.0-5.0) 2.0 (IQR: 0.0-5.5) 2.0 (IQR: 0.0-4.0) 0.20 (IQR: 0.06-0.60)	Normal control 0.0 (IQR: 0.0-1.8) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.03 (IQR: -0.15-0.17)	p>0.001† p = NS† p = 0.021† p = 0.005† p = 0.001† p<0.001† p = 0.006†	Post-Appliance 0.0 (IQR: 0.0-2.0) 0.0 (IQR: 0.0-0.5) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.0) 0.0 (IQR: 0.0-0.5) 0.0 (IQR: 0.0-1.0) 0.05 (IQR: -0.06-0.30)	Normal control NR	p = 0.03 p = NS p = NS p = NS p = NS p = NS p = NS	NA	YES

Reference	Year	Measures	Baseline			Post Treatment				Evidence treatment improves driving perf.?
			Treatment Group Mean (SD)	Control Group Mean (SD)	Between Groups Differences	Treatment Group Mean (SD)	Control Group Mean (SD)	Within Groups Differences*	Between Groups Differences	
Surgery –UPPP										
Haraldsson et al.(163)	1995	Brake reaction time Lateral position deviation Off-road events	Pre-surgery 1.88 (0.61) 40.0 (10.6) Median: 1 (Range: 0-69)	Normal controls 1.58 (0.23) 28.48 (6.9) Median: 0 (Range:0-2)	 p = NS‡ p = NS‡ p = NS‡	Post-Surgery 1.44 (0.61) 22.1 (5.74) Median: 0 (Range: 0-3)	Normal controls 1.38 (0.28) 21.7 (1.99) Median: 0 (Range: 0)	 p <0.05 p <0.01 p <0.01	 p = NS‡ p = NS‡ p = NS‡	YES (post-treatment similar to controls‡)

* CPAP treated group only

† Results of a comparison of controls to 20 OSA patients (prior to treatment group assignment)

‡ This is a very low power comparison – control group consisted of only 5 individuals

CI = Confidence interval; CPAP = Continuous positive airway pressure; IQR = Interquartile range; NA = Not applicable; NR = Not reported; NS = Not statistical; OSA = Obstructive sleep apnea; SD = Standard deviation; UPPP = Uvulopalatopharyngoplasty.

As stated above, eight included studies assessed the impact of CPAP on simulated driving performance, one study assessed the impact of medication, and one study assessed the impact of surgery on simulated driving performance. No included studies assessed the impact of behavioral modification on simulated driving performance. Consequently, we can draw no conclusions about the impact of behavioral modification on driving performance at this time.

Effect of CPAP on Simulated Driving Performance

Treatment of compliant individuals with moderate-to-severe OSA with CPAP improves driving performance (as measured by a number of different parameters tested on driving simulators and in one case, on a test track). All eight included studies that assessed the effect of CPAP on driving performance observed significant improvements from baseline levels across most parameters tested.

Effect of Medication on Simulated Driving Performance

Büttner and Rühle(160) studied the effect of theophylline 6mg/kg body weight versus an oral placebo tablet on sustained attention as measured by a simulated driving test. This study was undertaken with the premise that theophylline activates the awake-active neurons in the forebrain by antagonizing the effects of adenosine, and thus may alleviate the symptoms of daytime sleepiness and increase sustained attention. In this study, 39 male subjects with newly diagnosed OSA ingested active medication or placebo in a randomized order on two consecutive days. The computer-based driving simulation test (CarSim) was performed in a soundproof, darkened room and consisted of (1) steering the car to maintain one's lane (tracking); and (2) reacting to randomly appearing obstacles that were visible for only about 200 ms each. Tracking deviations decreased significantly from 49.3 ±99.5 s on placebo to 13.6 ±18.0 s on active drug. Improved performance was evident in 27 of the 39 study participants. The 12 subjects who did not improve on active medication were indistinguishable from those who did respond in terms of OSA characteristics such as AHI, leaving their nonresponse to the drug unexplained.

Effect of Oral Appliances on Simulated Driving Performance

Hoekema et al.(155) included three groups of subjects in their study; individuals with OSA who were utilizing CPAP (n = 10) or an oral appliance therapy (n = 9), and 16 healthy controls. Treatment subjects performed a pretreatment simulated driving test and then repeated the tests two to three months after initiation of therapy. Controls performed the test at similar time intervals. Individuals with OSA performed significantly worse than controls at the baseline visit. Following treatment, both the CPAP and OSA subjects improved significantly in terms of lapses of attention (LOA), and no significant differences were noted between the two treatment groups at the final review.

Effect of Surgery on Simulated Driving Performance

Haraldsson et al.(163) investigated the long-term effect of UPPP on vigilance and psychomotor function as measured on a simulated driving test in 13 male subjects. The simulated driving tests were administered as a presurgical baseline and at the 45-month postsurgery follow-up. Five non-apnea controls were also tested on two occasions to determine if any improvement in test scores occurred as a result of practice alone. Break reaction time (BRT), lateral position deviation (LPD), and a number of off-road incidents were assessed and found to have improved significantly postsurgery as compared with the presurgical values, even after the learning effect seen in controls was subtracted out.

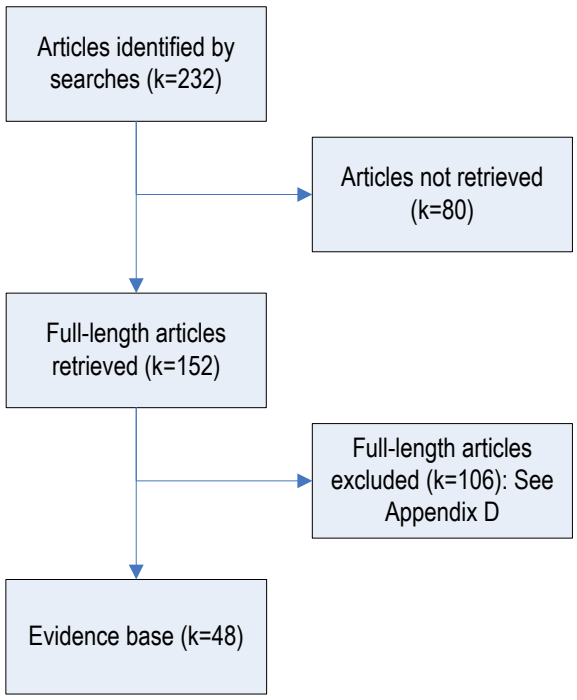
Key Question 5: Part C - Effect of Available Treatments on Indirect Measures of Driving Performance

In this subsection we examine the available evidence pertaining to the influence of available treatments for OSA on indirect measures of driving performance. The purpose of this section is to determine whether available treatments for OSA positively affect the indirect measures of driving performance.

Identification of Evidence Base

The process by which the evidence base for Key Question 5: Part C was identified is summarized in Figure 34. Our searches (Appendix A) identified a total of 232 articles that appeared to be relevant to this key question. Following application of the retrieval criteria (Appendix B) for this question, 152 full-length articles were retrieved and read in full. Of these 152 retrieved articles, 48 articles were found to meet the *a priori* inclusion criteria (Appendix C) for Key Question 5: Part C. Table D-5 of Appendix D lists the 106 articles that were retrieved but then excluded and lists the primary reason for their exclusion.

Figure 34. Development of Evidence Base for Key Question 5: Part C



Evidence Base for Key Question 5: Part C

Table 52 summarizes the treatments for OSA that were examined by the studies included in the evidence base. As can be seen, 32 included studies assessed the impact of CPAP on indirect measures of driving performance; 3 included studies assessed the impact of behavioral modification; 2 included studies assessed the impact of dental appliances; 8 included studies assessed the impact of medication; and 6 included studies assessed the impact of surgery.

Table 52. Evidence Base for Key Question 5: Part C

Reference	Year	Country	Behavioral modification	CPAP	Dental appliances	Medication	Surgery
Ballester et al.(164)	1999	Spain		✓			
Barbe et al.(99)	2001	Spain		✓			
Bardwell et al.(165)	2001	United States		✓			
Barnes et al.(166)	2004	Australia		✓	✓		
Barnes et al.(98)	2002	Australia		✓			
Becker et al.(167)	2003	Germany		✓			
Campos-Rodriguez et al.(168)	2006	Spain		✓			
Carly et al.(169)	2007	United States				✓	
Chakravorty et al.(170)	2002	United Kingdom		✓			
Coughlin et al.(171)	2007	United Kingdom		✓			
Engelman et al.(172)	1995	United Kingdom		✓			
Engelman et al.(105)	1997	United Kingdom		✓			
Engelman et al.(104)	1998	United Kingdom		✓			
Engelman et al.(103)	1999	United Kingdom		✓			
Engelman et al.(173)	1994	United Kingdom		✓			
Ferguson et al.(174)	2003	United Kingdom					✓
Hack et al.(162)	2000	United Kingdom		✓			
Haraldsson et al.(163)	1995	Sweden					✓
Haraldsson et al.(175)	1995	Sweden					✓
Hein et al.(176)	2000	Germany				✓	
Henke et al.(177)	2001	United States		✓			
Hirshkowitz et al.(178)	2006	United States/ Australia/Russia/ Germany/France				✓	
Hoekema et al.(155)	2006	Netherlands			✓		
Hui et al.(179)	2006	China		✓			
Jenkinson et al.(180)	1999	United Kingdom		✓			
Kaneko et al.(181)	2003	United States/ Canada		✓			
Kingshott et al.(100)	2004	New Zealand				✓	
Lojander et al.(182)	1996	Finland		✓			✓

Reference	Year	Country	Behavioral modification	CPAP	Dental appliances	Medication	Surgery
Lojander et al.(183)	1999	Finland		✓			✓
Loredo et al.(184)	2006	United States		✓			
Mansfield et al.(185)	2004	Australia		✓			
McArdale et al.(186)	2001	United Kingdom		✓			
Monasterio et al.(187)	2001	Spain		✓			
Montserrat et al.(188)	2001	Spain		✓			
Norman et al.(189)	2006	United States		✓			
Orbendorfer et al.(190)	2000	Austria				✓	
Orth et al.(158)	2005	Germany				✓	
Pack et al.(101)	2001	United States				✓	
Peppard et al.(191)	2000	United States	✓				
Robinson et al.(192)	2006	United Kingdom		✓			
Pepperell et al.(193)	2001	United Kingdom		✓			
Rasche et al.(194)	1999	Germany					
Ryan et al.(195)	2005	United States/Canada		✓		✓	
Sampol et al.(196)	1998	Spain	✓				
Schwartz et al.(197)	1991	United States	✓				
Usui et al.(198)	2005	Japan		✓			
Woodson et al.(199)	2003	United States		✓			✓
TOTALS =			**3**	**32**	**2**	**8**	**6**

CPAP = Continuous positive airway pressure.

Behavioral Modification and Indirect Measures of Driving Performance

Three studies examined for inclusion in the evidence base for Key Question 5 reported on the effect of behavioral modifications that were initiated in response to OSA diagnosis on indirect measures of driving performance. The primary attributes, quality assessment scores, generalizability table, and table of indirect measures assessed by the included studies in this subsection are found (respectively) in Table 53, Table 54, Table 55, and Table 56.

All three studies utilized a prospective study design in which individuals with OSA participated in behavioral modification (e.g., weight loss) to determine the effect this action might have on their AHI (k = 2) or SaO_2 levels (k = 1). The difference between their AHI rates or SAO_2 rates was calculated, and this outcome was assumed to be the consequence of treatment. The sample size of individuals enrolled in the included studies ranged from 24 to 690.

Table 53. Primary Attributes of Included studies that Examined the Impact of Behavioral Modification on Indirect Measures of Driving Performance

Reference	Year	Study Design	Method of Diagnosis	Prospective or Retrospective	Comparison of Interest	Study Population	Was compliance assessed?
Schwartz et al.(197)	1991	RCT	PSG	Prospective	CPAP + Weight Loss vs. CPAP + Usual Care	n = 26 Individuals with demonstrated disordered breathing rate >10 episodes/h	NR
Peppard et al.(191)	2000	Case Series Before After	PSG	Prospective	NA	n = 690 Participants in the Wisconsin Sleep Cohort Study (WSCS)	NA
Sampol et al.(196)	1998	Case Series Before After	PSG	Prospective	NA	n = 24 Individuals presently cured from a SAHS diagnosis	NA

NA = Not applicable; NR = Not reported; PSG = Polysomnogram; RCT = Randomized controlled trial; SAHS = Sleep apnea hypoapnea syndrome; WSCS = Wisconsin sleep cohort study.

Quality of Studies that Examined the Effects of Behavioral Modification on Indirect Measures of Driving Performance

The purpose of this subsection is to provide details regarding the quality of the included studies that address Key Question 5: Part C. This information is presented in Table 54. One of the studies was a moderate-quality RCT.(197) The remaining two studies (both of high quality) comprised before and after case series, which are susceptible to a variety of biases, including the possibility that individuals who enter a study and are aware of its purpose may not behave in the same manner as they did prior to entering the study. In addition, the small numbers found in two of the trials (n = 24; n = 26) may cause some concern when considering the possibility that the studies may have been statistically underpowered – that is, that they lacked the number of subjects sufficient to detect differences in treatment effect.(191,196) Of particular concern to this section, and to all the following sections, is the possibility of group differences arising from selection bias that was introduced through the mixing of patients populations with different OSA levels, as determined by measures such as AHI and daytime sleepiness (ESS, MSLT, and MWT).

Table 54. Quality of Included Studies that Examined Effect of Behavioral Modification on Indirect Measures of Driving Performance

Reference	Year	Instrument used	Quality
Schwartz et al.(197)	1991	ECRI Institute Quality Assessment Scale I: Randomized and Nonrandomized Studies	Moderate
Peppard et al.(191)	2000	ECRI Institute Quality Item Checklist for Single-Group Studies	High
Sampol et al.(196)	1998	ECRI Institute Quality Item Checklist for Single-Group Studies	High

Generalizability of Evidence to the Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 5: Part C are similar to CMV drivers in the United States. In general, the populations in these studies contain >50% males, between the ages of 30 and 60, who may present some similarities to the population predominantly found among CMV drivers in the United States. However, we cannot ascertain from these studies the extent of driving exposure in the participants, nor can we ascertain whether any of them were professional drivers. Thus, our ability to generalize beyond factors such as age or gender is limited. Other important characteristics of the individuals included in the studies that address Key Question 5: Part C are presented in Table 55.

Table 55. Generalizability of Included Studies that Examined Impact of Behavioral Modification on Indirect Measures of Driving Performance

Reference	Year	Type of Sleep Apnea	Mean Age	AHI (Mean, SD)	% Male	Driving Exposure	% CMV Drivers	Generalizability to target population
Schwartz et al.(197)	1991	OSA	Weight Loss Group 46.9 ±8.9 Usual Care Group 43.9 ±10.5	Non-REM DBR, episodes/hour Weight Loss Group 83.3 ±31.0 Usual Care Group 85.5 ±19.0	100	NR	NR	Unknown
Peppard et al.(191)	2000	OSA	46 ±7	Events/hour 4.1 ±9.1	56	NR	NR	Unknown
Sampol et al.(196)	1998	OSA	49.6 ±5.9	Diagnosis 44.3 ±27.8 Cure 3 ±3.1	88	NR	NR	Unknown

AHI = Apnea-hypopnea index; CMV = Commercial motor vehicle; DBR = Disordered breathing rate; NR = Not reported; OSA = Obstructive sleep apnea; REM = Rapid eye movement; SD = Standard deviation.

Findings of Studies that Assessed Behavioral Modification

Indirect Measures Assessed

Of the three included studies that evaluated the effect of behavioral modification an indirect measure of driver safety, two assessed the influence of behavioral modification on AHI, and one assessed the influence of behavioral modification on SaO_2 among individuals with OSA (Table 56).

Table 56. Indirect Measures Assessed by Included Studies that Examined Effect of Behavioral Modification on Indirect Measures of Driving Performance

Reference	Year	AHI	Daytime sleepiness	Cognitive and Psychomotor Function	Oxygen Saturation	Blood Pressure
Schwartz et al.(197)	1991				✓	
Peppard et al.(191)	2000	✓				
Sampol et al.(196)	1998	✓				
Totals		**2**	**0**	**0**	**1**	**0**

AHI = Apnea-hypopnea index.

Impact of Behavioral Modification on AHI

Peppard et al.(191) (Quality Score: High) and Sampol et al.(196) (Quality Score: High) both reported on the potential therapeutic effects of weight change on OSA. In Peppard et al. a prospective longitudinal study of the association of weight change and SDB, 690 randomly selected individuals underwent two evaluations at four-year intervals. These evaluations included obtaining anthropomorphic measures, such as height and weight; waist, neck, and hip girth; biceps, triceps, and suprailiac skinfolds ; the calculation of BMI; and a PSG. At the conclusion of the study, Peppard et al. found a relationship between weight gain and increase in SDB severity. Individuals who initially had mild or no SBD developed moderate to severe SBD with weight gain, while weight loss was associated with a reduction in both the severity of SBD and in the likelihood of developing SDB. In Sampol et al. a long-term follow-up study (94.3 ±27.4 months) of individuals who were considered "cured" of OSA through a combination of weight reduction, CPAP, or UPPP determined that the efficaciousness of weight loss on OSA remained in some individuals with OSA. Researchers also noted that periodic reinforcement of weight maintenance and early detection of OSA resumption could be managed with regular follow-up.

Impact of Behavioral Modification on SaO_2

Schwartz et al.(197) (Quality Score: Moderate) measured the effect of weight loss on apnea severity in patients with OSA. A population of 26 patients was invited to join a "weight loss group" that received intensive dietary counseling and behavior modification or a "usual care control group." While all patients were treated with CPAP, only the weight loss group was encouraged to lose 15% of body weight, a percentage associated with significant reductions in apnea severity. At baseline, no significant differences were found for SaO_2 between the weight loss group and usual care group (92.5 ±3.9 versus 93.7 ±2.2 respectively). A decrease in BMI in the weight loss group by 17.4 ±3.4% (mean ±SD) resulted in no significant change in baseline and average SaO_2, while a minimal increase in BMI (0.1 ±0.3%) in the usual care group resulted in a significant increase in baseline and average SaO_2 (p value = 0.019, p value = 0.01 respectively). Investigators concluded that improvement in oxyhemoglobin saturations for these apneic patients may have been a result of long-term treatment with CPAP.

CPAP and Indirect Measures of Driving Performance

A total of 32 studies examined for inclusion in the evidence base for Key Question 5: Part C reported on the effect of CPAP on indirect measures of driving performance among individuals with an OSA diagnosis. The primary attributes, quality assessment scores, generalizability table, and table of indirect measures assessed by the included studies in this subsection are found (respectively) in Table 57, Table 58, Table 59, and Table 60.

Table 57. Primary Attributes of Included Studies that Examined Effect of CPAP on Indirect Measures of Driver Safety

Reference	Year	Study Design	Method of Diagnosis	Prospective ?	Blinding status	Comparison of Interest	Study Population	Was compliance assessed?	Period over which data collected
Ballester et al.(164)	1999	RCT	NR	Yes	NB	CPAP vs. conservative treatment	n = 114 Individuals with OSA diagnosis requiring CPAP therapy	NR	3 months
Barbe et al.(99)	2001	RCT	PSG	Yes	DB	NR	n = 55 Individuals attending sleep units from August 1999 – March 2000	NR	NR
Bardwell et al.(165)	2001	RCT	PSG	Yes	SB	CPAP vs. Placebo	n = 36 Patients with a history suggestive of OSA with 100% to 150% of ideal body weight	NR	10 days
Barnes et al.(98)	2002	RCT-Crossover	PSG	Yes	SB	CPAP vs. Placebo	n = 28 Individuals referred for investigation of symptomatic sleep-disordered breathing	NR	16 weeks
Barnes et al.(166)	2004	RCT – Crossover	PSG	Yes	SB	CPAP vs. MAS vs. Placebo	n = 114 Individuals referred for investigation of symptomatic sleep-disordered breathing	43% compliant	3 months
Becker et al.(167)	2003	RCT	PSG	Yes	SB	CPAP vs. subtherapeutic CPAP	n = 60 Individuals with moderate to severe OSA	NR	9 weeks
Campos-Rodriguez et al.(168)	2006	RCT	NR	Yes	DB	CPAP vs. Placebo	n = 68 Individuals referred for investigation of symptomatic sleep-disordered breathing	NR	Baseline and 4 weeks following treatment
Chakravorty et al.(170)	2002	RCT	PSG	Yes	SB	CPAP vs. healthy lifestyle	n = 71 Individuals with evidence of moderate daytime sleepiness and AHI≥15/h	NR	3 months
Coughlin et al.(171)	2007	RCT – Crossover	PSG	Yes	DB	CPAP vs. subtherapeutic CPAP	n = 34 Individuals with OSA Naïve to CPAP No comorbidities	68% compliant	12 weeks
Engleman et al.(172)	1995	RCT – Crossover	PSG	Yes	SB	CPAP vs. Placebo	n = 13 Individuals with a minimum of 2 SAHS symptoms AHI ≥5/h slept during clinical PSG	67% compliant	3 weeks
Engleman et al.(105)	1997	RCT – Crossover	PSG	Yes	SB	CPAP vs. Placebo	n = 16 Individuals with two or more symptoms of SAHS AHI in the range 5.0 – 14.9/hour during PSG	50% compliant	8 weeks

Reference	Year	Study Design	Method of Diagnosis	Prospective ?	Blinding status	Comparison of Interest	Study Population	Was compliance assessed?	Period over which data collected
Engleman et al.(104)	1998	RCT – Crossover	PSG	Yes	SB	CPAP vs. Placebo	n = 23 Individuals with ≥15 apneas + hypopneas per hour ≥2 of eight symptoms of SAHS	NR	8 weeks
Engleman et al.(103)	1999	RCT – Crossover	PSG	Yes	SB	CPAP vs. Placebo	n = 34 Individuals with minimum SAHS symptoms, including significant sleepiness measured by ESS of >8 Admitted sleepiness while driving AHI range 5.0 – 14.9/h during PSG	NR	8 weeks
Engleman et al.(173)	1994	RCT – Crossover	PSG	Yes	SB	CPAP vs. Placebo	n = 32 Individuals with minimum of 2 SAHS symptoms	NR	8 weeks
Hack et al.(162)	2000	RCT	PSG	Yes	SB	CPAP vs. subtherapeutic CPAP	n = 59 Males aged of 30-75 with OSA ; ESS≥10 ≥10/hour dips in SaO_2 of >4% due to OSA	NR	1 month
Henke et al.(177)	2001	RCT	PSG	Yes	DB	CPAP vs. subtherapeutic CPAP	n = 46 Subjects with AHI>10/hour and daytime sleepiness	NR	6 weeks
Hui et al.(179)	2006	RCT	NR	Yes	DB	CPAP vs. Placebo	n = 100 Individuals with AHI≥5/hour OSA symptoms	57% compliant	Baseline and 3 months follow-up
Jenkinson et al.(180)	1999	RCT	PSG	Yes	DB	CPAP vs. subtherapeutic CPAP	n = 107 Males aged 30 – 75 years	NR	1 month
Kaneko et al.(181)	2003	RCT	PSG	Yes	SB	CPAP vs. control	n = 24 Individuals with OSA	NR	1 month
Lojander et al.(182)	1996	RCT	NR	Yes	NB	CPAP vs. UPPP	n = 76 Individuals aged 18 – 65 years Previously untreated OSA.	NR	12 months
Lojander et al.(183)	1999	RCT	PSG	Yes	NB	CPAP vs. UPPP	n = 50 Individuals with excessive daytime sleepiness, snoring, and witnessed apneas	90% compliant	12 months
Loredo et al.(184)	2006	RCT	PSG	Yes	DB	CPAP vs. Oxygen vs. Oxygen Supplement	n = 76 Individuals with AHI≥15 Suspicion of OSA	NR	2 weeks

Reference	Year	Study Design	Method of Diagnosis	Prospective ?	Blinding status	Comparison of Interest	Study Population	Was compliance assessed?	Period over which data collected
Mansfield et al.(185)	2004	RCT	PSG	Yes	NB	CPAP vs. control	n = 55 Individuals with AHI>5/hour and diagnosis of symptomatic, stable, and optimally treated congestive Heart Failure.	NR	3 months
McArdle et al.(186)	2001	RCT	PSG	Yes	DB	CPAP vs. Placebo	n = 23 Individuals with SAHS scheduled for CPAP treatment Two or more SAHS symptoms AHI>15/h (EEG-based study) or AHI>30/ (non-EEG based study)	NR	12 months
Monasterio et al.(187)	2001	RCT	PSG	Yes	DB	CPAP vs. conservative treatment (weight loss/sleep hygiene)	n = 66 CPAP treated patients n = 56 controls with mild SAHS	Yes - 64% compliance	6 months
Montserrat(188)	2001	RCT	PSG	Yes	DB	CPAP vs. placebo	n = 45 Individuals with: AHI ≤50/ESS <15 AHI >50/ESS <15 AHI ≤50/ESS ≥15 AHI >50/ESS ≥15	NR	6 weeks
Norman et al.(189)	2006	RCT	PSG	Yes	DB	CPAP vs. Oxygen vs. Placebo	n = 47 hypertensive adults aged 25-65 years	NR	2 weeks
Pepperell et al.(193)	2001	RCT	PSG	Yes	DB	CPAP vs. subtherapeutic CPAP	n = 118 Males with ESS score >9 and OSA	NR	4 weeks
Robinson et al.(192)	2006	RCT – Crossover	PSG	Yes	DB	CPAP vs. Subtherapeutic CPAP	n = 35 Nonsleepy, hypertensive individuals	Yes – Therapeutic CPAP mean use: 5.2 ±2.1/night; Sham CPAP mean use: 4.3 ±2.4/night	10 weeks
Ryan et al.(195)	2005	RCT	PSG	Yes	DB	CPAP plus optimal heart failure drug vs. optimal heart failure (HF) drug	n = 10 Individuals with history of HF of at least 6 months, left ventricular systolic dysfunction and AHI ≥20/hours of sleep	Yes – 100% compliance	1 month
Usui et al.(198)	2005	RCT	PSG	Yes	DB	CPAP vs. Control	n = 17 Individuals with severe OSA and heart failure	NR	1 month

Reference	Year	Study Design	Method of Diagnosis	Prospective ?	Blinding status	Comparison of Interest	Study Population	Was compliance assessed?	Period over which data collected
Woodson et al.(199)	2003	RCT – Crossover	PSG	Yes	Mixed: Investigators and Study coordinators: NB Sleep lab staff: Blinded Baseline assessment: DB Active vs. placebo: SB CPAP: NB	CPAP vs. Placebo	n = 90 Individuals aged 18 – 65 years Self-reports of daytime sleepiness BMI ≤34 kg/m^2 No prior surgical or CPAP treatment for OSA Mild to moderate OSA	37.5% objective compliance 77% subjective compliance	8 weeks

AHI = Apnea-hypopnea index; CPAP = Continuous positive airway pressure; DB = Double blinded; EEG = Electroencephalogram; ESS = Epworth sleepiness scale; HF = Heart failure; MAS = Mandibular advancement splint; NB = Not blinded; NR = Not reported; OSA = Obstructive sleep apnea;PSG = Polysomnogram; RCT = Randomized controlled trial; SAHS = Sleep apnea/hypoapnea score; SB = Single blinded; UPPP = Uvulopalatopharyngoplasty.

Quality of Studies Evidence Base

The purpose of this subsection is to provide details regarding the quality of the included studies that address Key Question 5: Part C. All 32 of the studies were RCTs; six of these were of moderate quality, two were judged to be of low quality, and one was of high quality. It should be noted that, while RCTs can help to control the possibility of bias introduced by differences in subject characteristics, the populations do differ in the severity of the AHI experienced by the study participants. Some participants had what the researchers termed moderate-severe AHI, while others had severe AHI. Comorbidities, such as congestive heart failure or left ventricular systolic dysfunction, existed in some studies that did not exist in others. Information about this quality assessment is presented in Table 58.

Table 58. Quality of Included studies that Examined Effect of CPAP on Indirect Measures of Driver Safety

Reference	Year	Instrument used	Quality
Ballester et al.(164)	1999	ECRI Institute Quality Assessment Scale I	Moderate
Barbe et al.(99)	2001	ECRI Institute Quality Assessment Scale I	High
Bardwell et al.(165)	2001	ECRI Institute Quality Assessment Scale I	High
Barnes et al.(166)	2004	ECRI Institute Quality Assessment Scale I	Moderate
Becker et al.(167)	2003	ECRI Institute Quality Assessment Scale I	Moderate
Campos-Rodriguez et al.(168)	2006	ECRI Institute Quality Assessment Scale I	High
Chakravorty et al.(170)	2002	ECRI Institute Quality Assessment Scale I	Moderate
Coughlin et al.(171)	2007	ECRI Institute Quality Assessment Scale I	High
Engleman et al.(105)	1997	ECRI Institute Quality Assessment Scale I	Moderate
Engleman et al.(104)	1998	ECRI Institute Quality Assessment Scale I	Low
Engleman et al.(103)	1999	ECRI Institute Quality Assessment Scale I	Moderate
Engleman et al.(173)	1994	ECRI Institute Quality Assessment Scale I	Moderate
Hack et al.(162)	2000	ECRI Institute Quality Assessment Scale I	High
Henke et al.(177)	2001	ECRI Institute Quality Assessment Scale I	Moderate
Hui et al.(179)	2006	ECRI Institute Quality Assessment Scale I	High
Jenkinson et al.(180)	1999	ECRI Institute Quality Assessment Scale I	High
Kaneko et al.(181)	2003	ECRI Institute Quality Assessment Scale I	Moderate
Loredo et al.(184)	2006	ECRI Institute Quality Assessment Scale I	Moderate
Mansfield et al.(185)	2004	ECRI Institute Quality Assessment Scale I	Low
Monasterio et al.(187)	2001	ECRI Institute Quality Assessment Scale I	Moderate
Montserrat et al.(188)	2001	ECRI Institute Quality Assessment Scale I	High
Norman et al.(189)	2006	ECRI Institute Quality Assessment Scale I	Moderate
Pepperell et al.(193)	2001	ECRI Institute Quality Assessment Scale I	High
Robinson et al.(192)	2006	ECRI Institute Quality Assessment Scale I	High
Ryan et al.(195)	2005	ECRI Institute Quality Assessment Scale I	Low
Usui et al.(198)	2005	ECRI Institute Quality Assessment Scale I	Moderate
Woodson et al.(199)	2003	ECRI Institute Quality Assessment Scale I	Low

Generalizability of Evidence Base to the Target Population

The samples included in the studies that address Key Question 5: Part C contain >50% males between the ages of 35 and 65, which may present some similarities to the population predominantly found among CMV drivers in the United States. However, we cannot ascertain from these studies the extent of driving exposure in the participants, or whether any of them were professional drivers. Thus, our ability to generalize beyond factors such as age or gender is limited. In fact, CMV drivers were excluded from two of the studies.(167,187) Other important characteristics of the individuals included in the studies that address Key Question 5: Part C are presented in Table 59.

Table 59. Generalizability of Included Studies that Examined Effect of CPAP on Indirect Measures of Driver Safety

Reference	Year	Severity of OSA	Mean Age (years)	AHI (Mean, SD)	BMI (kg/m^2)	% Male	Driving Exposure	% CMV Drivers	Generalizability to target population
Ballester et al.(164)	1999	Severe	CPAP: 53 ±13 Untreated: 54 ±1.5	56 ±20	CPAP: 32 ±0.6 Untreated: 34 ±1.2	CPAP: 88 Untreated: 86	NR	NR	Unknown
Barbe et al.(99)	2001	Severe	CPAP: 49 ±1 Control: 46 ±1	CPAP: 54 ±3 Control: 57 ±4	CPAP: 33 ±0.7 Control: 27 ±0.4	NR	Baseline (km driven, 1,000/year) Control 21 ±2 Cases 25 ±2	NR	Unknown
Bardwell et al.(165)	2001	NR	CPAP: 47 ±1.9 Placebo: 48 ±2.2	NR (Respiratory Disturbance Index or RDI: >15)	CPAP: 32.8 ±1.1 kg Placebo: 29.6 ±1.3 kg	80%	NR	NR	Unknown
Barnes et al.(166)	2004	Mild - Moderate	46.4 ±1.1 years	5 - 30	31.0 ±0.6 kg	80%	NR	NR	Unknown
Becker et al.(167)	2003	Moderate – Severe	CPAP: 54.4 ±8.9 Subtherapeutic CPAP: 52.3 ±8.4	CPAP: 62.5 ±17.8 Subtherapeutic CPAP: 65.0 ±26.7	CPAP: 33.3 ±5.1 Subtherapeutic CPAP: 33.5 ±6.0	91	NR	Excluded	Unknown
Campos-Rodriguez et al.(168)	2006	Moderate – Severe	55.3 ±9.6	CPAP: 58.3 ±24.6 Subtherapeutic CPAP: 59.5 ±21.7	35.7 ±5.6	55.8	NR	NR	Unknown
Chakravorty et al.(170)	2002	Moderate – Severe	CPAP: 49 ±11 Lifestyle: 52 ±9.6	CPAP: 55 ±28.7 Lifestyle: 35 ±19.1	CPAP: 40 ±14.5 Healthy Lifestyle: 40 ±12.8	NR	NR	NR	Unknown
Coughlin et al.(171)	2007	NR	49.0 ±8.3	NR (RDI: 39.7 ±13.8)	36.1 ±7.6	100	NR	NR	Unknown
Engleman et al.(105)	1997	Mild	52 ±2	5.0 – 14.9	29.8 ±1.8 kg	75%	NR	NR	Unknown
Engleman et al.(104)	1998	Moderate-Severe	47 ±12	≥15/hour	30 ±7	91	NR	NR	Unknown
Engleman et al.(103)	1999	Mild - Moderate	44 ±8	10 ±3/hour	30 ±5	62	NR	NR	Unknown
Engleman et al.(173)	1994	Mild - Severe	49 ±1.5	28	33 ±1.6	81	NR	NR	Unknown
Hack et al.(162)	2000	NR	50 median	NR	32.2	NR	31.5 years median	NR	Unknown

Reference	Year	Severity of OSA	Mean Age (years)	AHI (Mean, SD)	BMI (kg/m²)	% Male	Driving Exposure	% CMV Drivers	Generalizability to target population
Henke et al.(177)	2001	Moderate – Severe	CPAP: 50.2 ±10.4 Subtherapeutic: 50.6 ±9.7	CPAP: 62.1 ±27.4 Subtherapeutic: 68.1 ±25.2	CPAP: 42.7 ±10.5 Subtherapeutic: 42.2 ±11.9	55	NR	NR	Unknown
Hui et al.(179)	2006	Severe	50.2	31.2 (16.46)	27.4	82.6	NR	NR	Unknown
Jenkinson et al.(180)	1999	NR	CPAP: 50 (33-71) Subtherapeutic: 48 (36-68)	NR	CPAP: 35.1 (25.8-44.3) Subtherapeutic: 35.0 (26.9-51.4)	100	NR	NR	Unknown
Kaneko et al.(181)	2003	Moderate – Severe	CPAP: 55.9 ±2.5 Control: 55.2 ±3.6	CPAP: 37.1 ±6.4 Control: 45.2 ±5.3	30.4 ±0.7	92	NR	NR	Unknown
Loredo et al.(184)	2006	Moderate - Severe	CPAP: 48.2 ±10.9 Placebo: 48.3 ±11.2	≥15	CPAP: 31.8 ±5.5 kg Placebo: 31.8 ±6.8 kg	80%	NR	NR	Unknown
Mansfield et al.(185)	2004	Moderate – Severe	CPAP: 57.2 ±1.7 Control: 57.5 ±1.6	CPAP: 29.3 ±0.4 Control: 28.1 ±3.9	CPAP: 33.5 ±0.9 kg Control: 34.6 ±1.2 kg	100	NR	NR	Unknown
Monasterio et al.(187)	2001	Mild	CPAP: 53 ±9 Conservative Lifestyle: 54 ±9	CPAP: 20 ±6 Conservative Lifestyle: 21 ±6	CPAP: 29.4 ±3.7 kg Conservative Lifestyle: 29.5 ±3.3 kg	81	NR	Excluded	Unknown
Montserrat et al.(188)	2001	Severe	CPAP: 55.65 ±9.41 Sham CPAP: 52.59 ±10.93	CPAP: 50.52 ±19.83 Subtherapeutic: 57.14 ±21.14	CPAP: 30.31 ±4.49 Sham CPAP: 33.73 ±6.62	NR	NR	NR	Unknown
Norman et al.(189)	2006	Moderate – Severe	Placebo: 49.3 ±2.7 CPAP: 49.7 ±2.5	Placebo: 59.2 ±9.3 CPAP: 66.1 ±8.8	31.5 ±1.4	80	NR	NR	Unknown
Pepperell et al.(193)	2001	Moderate – Severe	CPAP: 50.1 ±10.4 Subtherapeutic CPAP: 51.0 ±9.8	CPAP: 8.9 ±7.3 Subtherapeutic: 28.4 ±15.0	CPAP: 34.6 ±8.5 kg Subtherapeutic CPAP: 35.3 ±6.0 kg	100	NR	NR	Unknown
Robinson et al.(192)	2006	NR	54 ±8	NR	33.2 ±5.3	88	NR	NR	Unknown
Ryan et al.(195)	2005	Moderate – Severe	CPAP: 57.6 ±2.2 Control: 60.3 ±1	CPAP: 29.3 ±4.8 Control: 57.9 ±5.5	CPAP: 28.3 ±1.3 kg Control: 35.1 ±3.7 kg	89	NR	NR	Unknown
Usui et al.(198)	2005	Moderate – Severe	CPAP: 55.2 ±2.0 Control: 52.2 ±4.1	CPAP: 40.4 ±7.9 Heart Failure Drug Therapy: NR	CPAP: 29.9 ±1.5 Control: 31.3 ±1.6	88	NR	NR	Unknown
Woodson et al.(199)	2003	Moderate – Severe	CPAP: 51.7 ±8.6 years Placebo: 46.0 ±8.1	CPAP: 21.3 ±11.1 Placebo: 15.4 ±7.8	CPAP: 29.1 ±3.7 kg Placebo: 28.5 ±4.2 kg	80%	NR	NR	Unknown

AHI = Apnea-hypopnea index; BMI = Body mass index; CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; NR = Not reported; OSA = Obstructive sleep apnea; RDI = Respiratory disturbance index; SD = Standard deviation.

Findings

The indirect measures assessed by each of the 27 included studies are presented in Table 60.

Table 60. Indirect Measures assessed by included studies that examined effect of CPAP on OSA severity/AHI

Reference	Year	AHI	Daytime Sleepiness	Cognitive and Psychomotor Function	Oxygen Saturation	Blood Pressure
Ballester et al.(164)	1999		✓	✓		
Barbe et al.(99)	2001		✓	✓		✓
Bardwell et al.(165)	2001			✓	✓	
Barnes et al.(166)	2004		✓	✓	✓	✓
Becker et al.(167)	2003	✓	✓		✓	✓
Campos-Rodriguez et al.(168)	2006					✓
Chakravorty et al.(170)	2002	✓	✓			
Coughlin et al.(171)	2007		✓			✓
Engleman et al.(105)	1997		✓	✓		
Engleman et al.(104)	1998		✓	✓		
Engleman et al.(103)	1999		✓	✓		
Engleman et al.(173)	1994		✓	✓		
Hack et al.(162)	2000		✓			
Henke et al.(177)	2001	✓	✓		✓	
Hui et al.(179)	2006		✓		✓	✓
Jenkinson et al.(180)	1999		✓			
Kaneko et al.(181)	2003	✓			✓	✓
Loredo et al.(184)	2006				✓	
Mansfield et al.(185)	2004	✓	✓		✓	✓
Monasterio et al.(187)	2001	✓	✓	✓		✓
Montserrat et al.(188)	2001		✓			
Norman et al.(189)	2006	✓			✓	✓
Pepperell et al.(193)	2001	✓				✓
Robinson et al.(192)	2006					✓
Ryan et al.(195)	2005	✓			✓	✓
Usui et al.(198)	2005					✓
Woodson et al.(199)	2003		✓			
Totals	**27**	**9**	**18**	**9**	**10**	**14**

AHI = Apnea-hypopnea index.

In summary, 9 articles assessed the impact of treatment with CPAP on the severity of disordered respiration; 18 measured the impact of CPAP on daytime sleepiness; 9 assessed the impact of the technology on cognitive and psychomotor function; 10 assessed the impact of CPAP on SaO_2; and 14 measured the impact of CPAP on blood pressure.

Impact of CPAP on Severity of Disordered Respiration during Sleep

Nine included studies (Quality Rating: Moderate) reported on the effects of CPAP on the severity of disordered respiration during sleep. All nine assessed this outcome using the AHI. The findings of these studies are summarized in Table 61.

Table 61. Impact of CPAP on AHI

Reference	Year	Outcome Assessed	FUT	TG Size (n =)	TG Mean (SD)	CG Size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
Norman et al.(189)	2006	AHI (events/hour)	2 weeks	18	3.4 (3.0)	15	50.1 (32.1)	-46.700 (-61.559, -31.841)	0.000
Ryan et al.(195)	2005	AHI (events/hour)	1 month	10	6.1 (SE: 1.1)	8	56.2 (SE: 5.3)	-50.100 (-59.632, -40.568)	0.000
Mansfield et al.(185)	2004	AHI (events/hour)	3 months	19	2.9 (SE: 0.8)	21	18.2 (SE: 2.8)	-15.300 (-21.266, -9.334)	0.000
Becker et al.(167)	2003	AHI (events/hour)	3 months*	16	3.4 (3.1)	16	33.4 (29.2)	-30.000 (-87.553, 27.553)	0.307
Kaneko et al.(181)	2003	AHI (events/hour)	1 month	12	3.6 (SE: 0.7)	12	36.1 (SE: 5.6)	-32.500 (-43.561, -21.439)	0.000
Chakravorty et al.(170)	2002	AHI (events/hour)	3 months	32	8.0 (28.0)	21	34.0 (21.0)	-26.000 (-40.028, -11.972)	0.000
Henke et al.(177)	2001	AHI (events/hour)	2 weeks*	18	5.1 (6.2)	27	64.9 (26.2)	-59.800 (-70.037, -49.563)	0.000
Monasterio et al.(187)	2001	AHI (events/hour)	6 months	66	6.0 (8.0)	59	17.0 (10.0)	-11.000 (-14.160, -7.840)	0.000
Pepperell et al.(193)	2001	AHI (events/hour)	4 weeks	53	8.9 (7.3)	51	28.4 (15.0)	-19.500 (-24.005, -14.995)	0.000

* Approximate

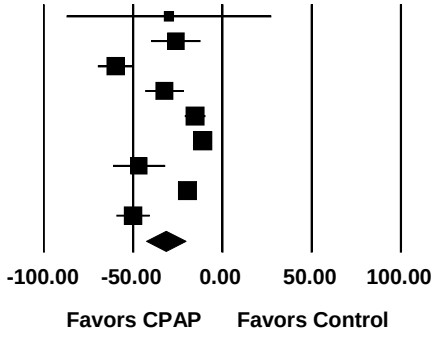
AHI = Apnea-hypopnea index; CG = Control group; FUT = Follow-up time; SD = Standard deviation; SE = Standard error; TG = Treatment group; WMD = Weighted mean difference.

The findings of the nine included studies were reasonably consistent in that they all found that AHI was decreased following CPAP therapy. While all studies observed the same direction of effect, there were, however, large differences between studies in the magnitude of treatment effectiveness. A formal quantitative assessment of these data for consistency (homogeneity testing) found that the results of the nine studies were heterogeneous ($q = 147.95$, $p < 0.0001$: $I2 = 94.59$). Because we refrain from exploring heterogeneity using meta-regression when the evidence base consists of fewer than 10 studies per covariate, the source (or sources) of heterogeneity in this evidence base has not been established. Consequently we were precluded from combining the data into a fixed-effects meta-analysis in order to obtain a single point estimate of the effect of CPAP on AHI.

In order to obtain a more general estimate of the impact of CPAP on AHI, we pooled the data using a random-effects meta-analysis. The results of this analysis are presented in Figure 35. These results indicate that, on average, CPAP reduced the incidence of apneic/hypopneic episodes by approximately 32 (CI 95%: 42.95, 20.83) per hour. A series of sensitivity analyses (see Appendix H) found this finding to be robust.

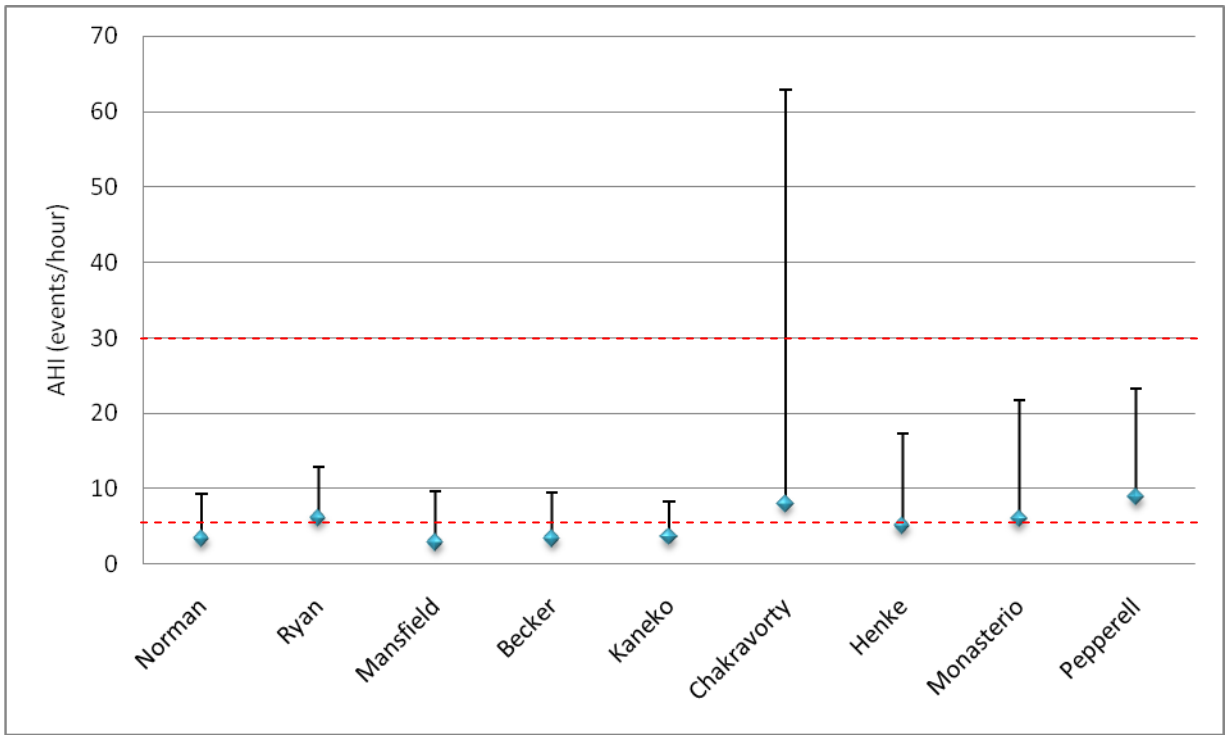
Figure 35. REMA – Effect of CPAP on OSA Severity as Defined by AHI

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	Z-Value	p-Value
Becker	-30.000	29.364	862.250	-87.553	27.553	-1.022	0.307
Chakravorty	-26.000	7.157	51.225	-40.028	-11.972	-3.633	0.000
Henke	-59.800	5.223	27.280	-70.037	-49.563	-11.449	0.000
Kaneko	-32.500	5.643	31.847	-43.561	-21.439	-5.759	0.000
Mansfield	-15.300	3.044	9.264	-21.266	-9.334	-5.027	0.000
Monasterio	-11.000	1.612	2.599	-14.160	-7.840	-6.823	0.000
Norman	-46.700	7.581	57.479	-61.559	-31.841	-6.160	0.000
Pepperell	-19.500	2.299	5.283	-24.005	-14.995	-8.484	0.000
Ryan	-50.100	4.863	23.650	-59.632	-40.568	-10.302	0.000
	-31.897	5.642	31.835	-42.956	-20.839	-5.653	0.000



Although it is clear that CPAP reduces the severity of disordered respiration during sleep, the findings above do not tell us whether CPAP is so effective that it reduces AHI levels to normal levels. Figure 36 shows mean AHI and its 95% confidence intervals of the enrollees in each of the 9 included studies following treatment. It can be seen that while CPAP is clearly effective, many individuals will have an AHI ≥5 (mild OSA), and some may even have an AHI ≥30 (severe OSA).

Figure 36. Impact of CPAP on AHI at Final Follow-up



Impact of CPAP on Blood Pressure

Fourteen included studies measured the impact of CPAP on blood pressure. Several different measures of blood pressure were measured. These included 24-hour systolic blood pressure, 24-hour diastolic blood pressure, diurnal blood pressure, and nocturnal blood pressure. In this report we report on the findings of 2 of these outcome measures: 24-hour systolic blood pressure and 24-hour diastolic blood pressure.

Impact of CPAP on 24-Hour Systolic Blood Pressure

Ten included studies (Overall Quality Rating: Moderate) reported on the effects of CPAP on 24-hour systolic blood pressure as associated with OSA. The findings of these studies are summarized in Table 62.

Table 62. Effect of CPAP on 24-hour Systolic Blood Pressure

Reference	Year	FUT	TG Size (n =)	TG Mean (SD)	CG Size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
Barbe et al.(99)	2001	6 weeks	29	124.2 (10.7)	25	122.3 (15)	1.900 (4.998, 8.798)	0.589
Becker et al.(167)	2003	9 weeks (on average)	16	126.4 (14.3)	16	137.3 (11.1)	-10.90 (-19.770, -2.029)	0.016
Campos-Rodriguez et al.(168)	2006	4 weeks	34	131.3 (12.1)	34	129.8 (16.3)	1.50 (-5.323, 8.323)	0.667
Coughlin et al.(171)	2007	6 weeks	34	135.7 (11.6)	34	142.2 (13.994)	-6.50 (-12.622, -0.377)	0.037
Hui et al.(179)	2006	12 weeks	23	125.9 (14.3)	23	122.0 (14.3)	3.900 (-4.364, 12.164)	0.355
Kaneko et al.(181)	2003	4 weeks	12	116 (20.7)	12	134 (27.71)	-18.000 (-37.596, 1.596)	0.072
Monasterio et al.(187)	2001	3 months	66	122 (22)	59	130 (16)	-8.000 (-14.813, -1.186)	0.021
Pepperell et al.(193)	2002	4 weeks	59	130.2 (14.594)	59	135.9 (17.666)	-5.700 (-11.546, 0.146)	0.056
Robinson et al.(192)	2006	1 month	16	137.0 (16.3)	16	139.3 (17.6)	-2.300 (-14.054, 9.454)	0.701
Usui et al.(198)	2005	1 month	8	119.5 (15.556)	9	145.7 (27.3)	-26.200 (-47.716, -4.683)	0.017

CG = Control group; FUT = Follow-up time; SD = Standard deviation; TG = Treatment group; WMD = Weighted mean difference.

Unlike the findings of AHI, there appears to be little agreement between included studies on the impact of CPAP on 24-hour systolic blood pressure. Homogeneity testing found that the findings of the 10 studies differed from one another by a magnitude that is greater than one expects to see by chance alone ($q = 19.55$, $p < 0.0001$; $I2 = 53.98$). Consequently, we were precluded from combining the data from these studies in a fixed-effects meta-analysis in order to obtain a single-point estimate of CPAP effects on 24-hour systolic blood pressure among individuals with OSA.

Because the evidence base consisted of 10 studies, we explored the heterogeneity using meta-regression. Because we require at least 10 studies per covariate included in our meta-regression models, our exploration consisted of univariable meta-regressions: no multivariable meta-regressions were

performed. Each of the covariates considered in these analyses and the findings of each meta-regression we performed are presented in Table 63.

Table 63. Findings – CPAP and Systolic Blood Pressure Univariate Meta-regression Analyses (unrestricted maximum likelihood model)

Covariate	Coefficient	95% CI	p =	Coefficient significant?	Residual	Model	Total	Tau²
Patient Level Covariates								
Mean Age	0.78083	-1.71 to 1.34	0.81303	No	q = 12,31165 p = 0.13783	q = 0.05594 p = 0.81303	q = 12.36760 p = 0.19337	13.51936
% Male	0.10256	-0.40 to -0.00	0.04944	No	q = 12.70686 p = 0.4977	q = 3.84924 p = 0.04977	q = 16.55609 p = 0.05614	3.74291
BMI	0.54517	-1.39 to 0.74	0.55206	No	q = 13.19673 p = 0.10526	q = 0.35365 p = 0.55206	q = 13.55038 p = 0.13924	9.92755
OSA Severity	NC	NC	NC	NC	NC	NC	NC	NC
Study level covariates								
Time studied	4.32515	-13.35 to 3.60	0.25967	No	q = 10.27453 p = 0.24628	q = 1.27052 p = 0.25967	q = 11.54505 p = 0.24019	16.60489

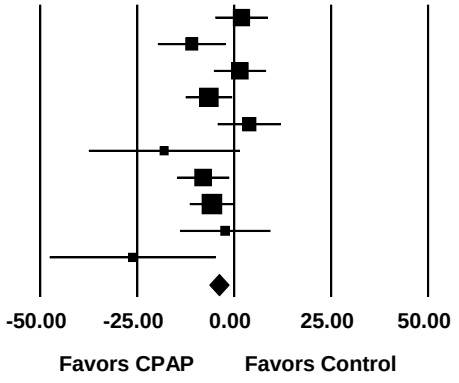
BMI = Body mass index; NC = Not calculated because necessary data were not reported by all included studies; OSA = Obstructive sleep apnea.

Our meta-regression did not find any of the covariates examined to be significantly correlated with 24-hour systolic blood pressure. Consequently, our analyses did not explain why the results of the included studies differed from one another. The unexplained quantitative inconsistency in these data precludes one from determining a single estimate of the effect of CPAP on 24-hour systolic blood pressure in individuals with OSA.

In order to obtain an estimate of the overall impact of CPAP on 24-hour systolic blood pressure, we pooled the data from each the 10 included studies using random-effects meta-analysis. The findings of this analysis are presented in Figure 37.

Figure 37. REMA - CPAP and 24-Hour Systolic Blood Pressure

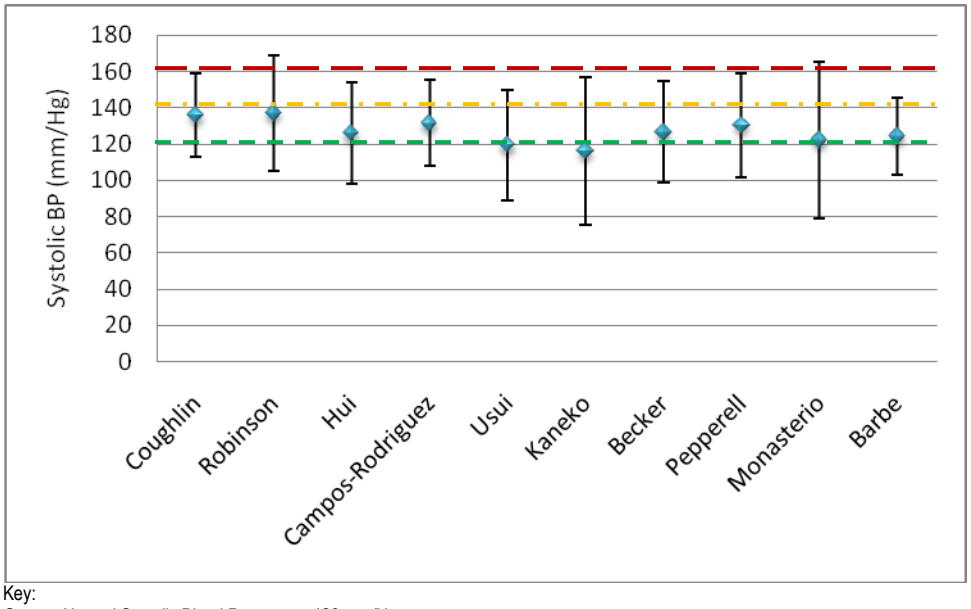
Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barbe	1.900	3.519	12.387	-4.998	8.798	0.540	0.589
Becker	-10.900	4.526	20.481	-19.770	-2.030	-2.409	0.016
Campos-Rodriguez	1.500	3.481	12.121	-5.324	8.324	0.431	0.667
Coughlin	-6.500	3.124	9.759	-12.623	-0.377	-2.081	0.037
Hui	3.900	4.217	17.782	-4.365	12.165	0.925	0.355
Kaneko	-18.000	9.999	99.971	-37.597	1.597	-1.800	0.072
Monasterio	-8.000	3.476	12.086	-14.814	-1.186	-2.301	0.021
Pepperell	-5.700	2.983	8.900	-11.547	0.147	-1.911	0.056
Robinson	-2.300	5.997	35.966	-14.054	9.454	-0.384	0.701
Usui	-26.200	10.978	120.515	-47.716	-4.684	-2.387	0.017
	-4.029	1.278	1.634	-6.534	-1.523	-3.152	0.002



The results indicate that, on average, CPAP does reduce 24-hour systolic blood pressure scores. This reduction is in the order of 4.49 (CI 95%: 8.43, 0.54) mmHg. A series of sensitivity analyses (Appendix H), however, found that this finding is not robust, which weakens the confidence we have in our findings.

Although the available evidence suggests that CPAP reduces 24-hour systolic blood pressure, the findings above do not tell us whether CPAP is so effective that it improves systolic blood pressure to normal levels. Figure 38 shows the mean 24-hour blood pressure and 95% confidence intervals of the enrollees in each of the 10 included studies at final follow up. It can be seen that while CPAP may be effective, some individuals will still experience high systolic blood pressure.

Figure 38. Impact of CPAP on 24-hour Systolic Blood Pressure at Final Follow-up



Key:
Green: Normal Systolic Blood Pressure, <120 mm/Hg
Yellow: Upper limit of Prehypertension, 121-139 mm/Hg
Red: Upper limit of Stage I Hypertension, 140 – 159 mm/Hg

Impact of CPAP on 24-hour Diastolic Blood Pressure

Ten included studies (Quality Rating: Moderate) reported on the effects of CPAP on 24-hour diastolic blood pressure as associated with OSA. The findings of these studies are summarized in Table 64.

Table 64. Findings – Effect of CPAP on 24-hour Diastolic Blood Pressure

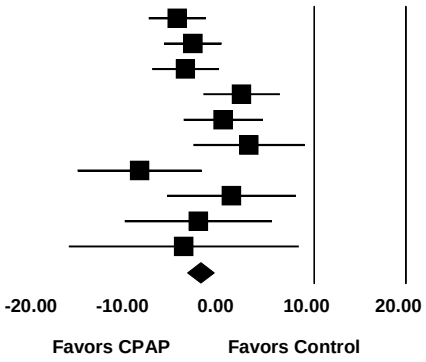
Reference	Year	FUT	TG size (n =)	TG Mean (SD)	CG size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
Becker et al.(167)	2003	9 weeks (on average)	16	73.1 (10.5)	16	82.1 (9.1)	-9.000 (-15.808, -2.192)	0.010
Coughlin et al.(171)	2007	6 weeks	34	86.8 (0.87)	34	91.7 (9.3)	-4.900 (8.049, -1.751)	0.002
Usui et al.(198)	2005	1 month	8	62.6 (14.4)	9	66.8 (12.0)	-4.200 (-16.759, 8.359)	0.512
Monasterio et al.(187)	2001	3 months	66	80.0 (10.0)	59	84.0 (11.0)	-4.000 (-7.681, -0.319)	0.033
Pepperell et al.(193)	2002	4 weeks	59	82.7 (9.2)	59	85.9 (8.4)	-3.200 (-6.391, -0.009)	0.049
Robinson et al.(192)	2006	1 month	16	84.2 (11.7)	16	86.8 (11.6)	-2.599 (-10.673, 5.473)	0.528
Campos-Rodriguez et al.(168)	2006	4 weeks	34	76.9 (9.3)	34	76.8 (9.0)	0.100 (-4.250, 4.450)	0.964
Kaneko et al.(181)	2003	4 weeks	12	59.0 (6.9)	12	58.0 (10.3)	1.000 (-6.067, 8.067)	0.782
Barbe et al.(99)	2001	6 weeks	29	79.1 (5.3)	25	77.0 (10.0)	2.100 (-2.104, 6.304)	0.328
Hui et al.(179)	2006	12 weeks	23	82.5 (10.5)	23	79.6 (10.5)	2.900 (-3.197, 8.997)	0.351

CG = Control group; FUT = Follow-up time; SD = Standard deviation; TG = Treatment group; WMD = Weighted mean difference.

Homogeneity testing of the data presented in the table above found that the differences in the findings of the 10 included studies did not differ by greater than that which one would expect to see by chance alone (Q = 16.54; p<0.0001; I^2 = 45.59). Consequently, we pooled these data using a fixed-effects meta-analysis with the aim of determining a single-point estimate of the magnitude of the impact of CPAP on 24-hour diastolic blood pressure (Figure 39).

Figure 39. FEMA - CPAP and 24-hour Diastolic Blood Pressure

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Coughlin	-4.900	1.607	2.582	-8.049	-1.751	-3.049	0.002
Pepperell	-3.200	1.628	2.651	-6.391	-0.009	-1.965	0.049
Monasterio	-4.000	1.878	3.528	-7.681	-0.319	-2.130	0.033
Barbe	2.100	2.145	4.601	-2.104	6.304	0.979	0.328
Campos-Rodriguez	0.100	2.219	4.926	-4.250	4.450	0.045	0.964
Hui	2.900	3.111	9.678	-3.197	8.997	0.932	0.351
Becker	-9.000	3.474	12.066	-15.808	-2.192	-2.591	0.010
Kaneko	1.000	3.605	12.999	-6.067	8.067	0.277	0.782
Robinson	-2.600	4.119	16.966	-10.673	5.473	-0.631	0.528
Usui	-4.200	6.408	41.061	-16.759	8.359	-0.655	0.512
	-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001



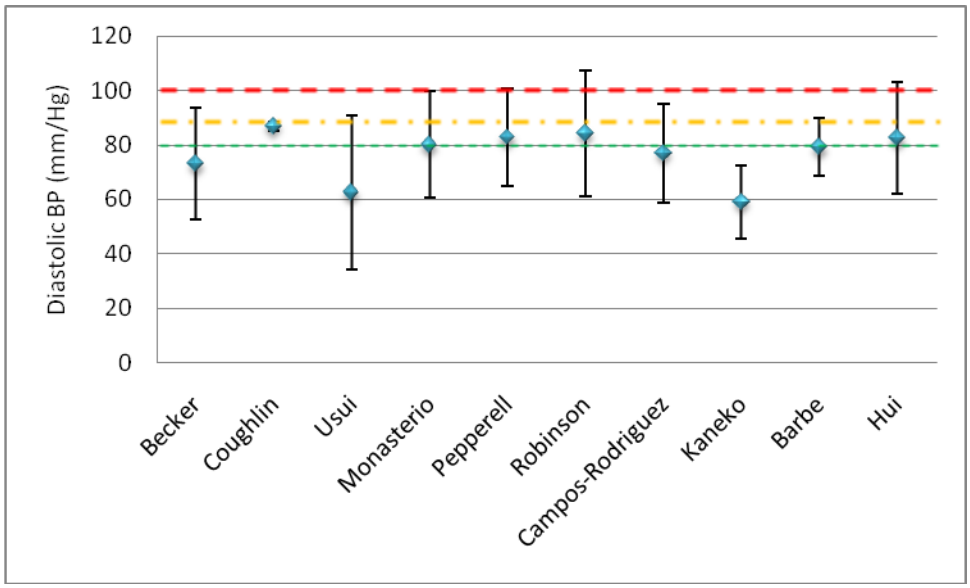
Meta Analysis

The results of this analysis indicate that, on average, CPAP decreased diastolic blood pressure levels by 2.41 mmHg (CI 95%: 0.96 mmHg – 3.87 mmHg). A series of sensitivity analyses (Appendix H) found our findings to be qualitatively robust (changes in our original assumptions did not change the direction of effect). However, our findings were not quantitatively robust (changes in our assumptions led to large changes in the magnitude of effect). Consequently, while we can be reasonably confident that CPAP reduces 24-hour diastolic blood pressure, our confidence in the magnitude of this benefit is diminished.

Although the available evidence suggests that CPAP reduces 24-hour diastolic blood pressure, the findings above do not tell us whether CPAP is so effective that it improves diastolic blood pressure to

normal levels. Figure 40 shows the mean 24-hour diastolic blood pressure and 95% confidence intervals for the enrollees in each of the 10 included studies at final follow-up. It can be seen that while CPAP may be effective, some individuals will still experience high diastolic blood pressure.

Figure 40. Impact of CPAP on 24-hour Diastolic Blood Pressure at Final Follow-up



Key:
Green: Normal, <80 mm/Hg
Yellow: Stage I Hypertension, 90-99 mm/Hg
Red: Stage II Hypertension, ≥100 mm/Hg

Impact of CPAP on Cognitive and Psychomotor Function

Eleven included studies (Quality Rating: Moderate) reported on the impact of CPAP on measure of cognitive and psychomotor function. The findings of these studies are summarized in Table 65.

Table 65. Cognitive and Psychomotor Function Following CPAP Administration

Reference	Year	Test	Scale	CPAP	Control	p =	Summary
Barbe et al.(99)	2001	SteerClear	Hits (%)	4 ±1	5 ±2	>0.200	Cognitive Function
		Wechsler Adult Intelligence test	Digit symbols	43 ±3	47 ±4	>0.200	Pretreatment: similar in both groups
			Block design	34 ±1	33 ±2	>0.200	Post-treatment: no significant change.
			Digit span	9 ±0.3	10 ±1	>0.200	
		PASAT (1-4)†	1	15 ±1	15 ±1	>0.200	
			2	16 ±1	15 ±1	0.040	
			3	12 ±1	12 ±1	0.090	
			4	5 ±1	5 ±1	>0.200	
		Trail making test	Part A	47 ±3	47 ±3	>0.200	
			Part B	96 ±6	110 ±10	0.100	
		Wechsler Memory Scale		6 ±0.4	7 ±0.4	>0.200	
		Verbal Paired associated		15 ±1	15 ±1	>0.200	
Bardwell et al.(165)	2001	Digit Symbol		53.5 ±3.0	53.2 ±2.5	NR	Post-treatment: CPAP group had significantly better overall cognitive functioning when compared to placebo group.
		Trail making test	Part A	27.4 ±2.0	27.4 ±1.6		
			Part B	87.0 ±8.7	71.2 ±7.1		
		Trail making test	Part A (errors)	0.2 ±0.1	0.03 ±0.1		
			Part B (errors)	1.1 ±0.3	0.5 ±0.2		
		Digit Vigilance	Time	6.6 ±0.4	6.9 ±0.3		
			Errors	12.3 ±3.1	10.2 ±2.6		
		Digit Span	Forward	8.7 ±0.7	8.6 ±0.6		
			Backward	6.4 ±0.8	7.7 ±0.8		
			Total	15.1 ±1.3	16.2 ±1.1		
		Stroop naming	Correct	82.2 ±3.2	80.3 ±2.7		
			Errors	0.3 ±0.1	0.1 ±0.1		
		Stroop reading	Correct	92.8 ±2.3	95.6 ±2.0		
			Errors	0.01 ±0.1	0.1 ±0.1		
		Stroop interference	Correct	41.0 ±2.1	44.2 ±1.8		
			Errors	0.8 ±0.3	0.3 ±0.3		
		Word Fluency	Correct	37.3 ±3.2	44.5 ±2.7		
			Preservations	1.2 ±0.3	0.8 ±0.3		
			Intrusions	0.4 ±0.2	0.1 ±0.1		
			Variations	0.8 ±0.3	0.6 ±0.2		
		Digit Ordering	Correct	86.1 ±2.0	90.6 ±1.7		
			Errors	2.7 ±0.8	4.9 ±0.7		

Reference	Year	Test	Scale	CPAP	Control	p =	Summary
Barnes et al.(166)	2004	Digit span	Backward	4.6 (0.1)	4.8 (0.1)	NR	Improvements observed • CPAP: increased vigilance • CPAP and MAS: improved executive cognitive function (PASAT)
		Trail making test	B	73.3 (3.3)	74.2 (3.6)		
		Digit symbol	substitution task	47.3 (0.4)	46.8 (0.4)		
		COWAT‡		46.5 (1.2)	46.3 (1.0)		
		PVT*	Lapses	2.1 (0.2)	2.7 (0.3)		
		Stroop color association test		9.3 (0.9)	9.2 (0.9)		
		PASAT		2.9 (0.1)	3.4 (0.1)		
Barnes et al.(98)	2002	Word Pair Memory Recall		+0.4	+.05	NR	Improvements reported CPAP: verbal fluency (COWAT) and vigilance (Psychomotor Vigilance Task) CPAP and Placebo: Trailmaking B task improved but neither was significantly better than baseline.
		WMS-R Visual Reproduction**		+1.2	+1.6		
		Trail making test	Part A	-0.1	-0.6		
			Part B	-5.2	-0.1		
		Digit Symbol Substitution		+0.8	+1.5		
		COWAT		+3.4	+0.7		
		Psychomotor Vigilance Task		-0.1	-0.1		
		Stroop Color Association		+2.2	+1.0		
Engleman et al.(105)	1997	FULL GROUP - CPAP VERSUS PLACEBO					Improved Performance CPAP: TrailMaking B task of mental flexibility CPAP subgroup comparison of poor versus compliant users: TrailMaking B task.
		Trail making test	Part B	64.1 (5.5)	77.7 (9.2)	0.020	
		SteerClear	Hits	74.8 (7.3)	75.3 (8.9)	NS	
		PASAT (2 sec rate)	Correct	37.8 (3.3)	35.3 (2.8)	NS	
		RVIPT#	Correct	36.9 (3.5)	34.8 (3.2)	NS	
		Median eight-choice reaction time	ms	365 (16)	356 (14)	NS	
		Verbal fluency (total words)	Total Words	38.5 (3.5)	39.2 (3.1)	NS	
		BVRT∞	Correct	7.3 (0.6)	7.3 (0.6)	NS	
		BETTER CPAP COMPLIERS - CPAP VERSUS PLACEBO					
		Trail making test	Part B	61.9 ±9.1	76.1 ±14.1	0.040	
		SteerClear	Hits	81.7 ±12.1	83.7 ±13.1	NS	
		PASAT (2 sec rate)	Correct	37.4 ±5.7	33.3 ±4.1	NS	
		RVIPT	Correct	34.4 ±3.5	36.6 ±4.0	NS	
		Median eight-choice reaction time	ms	386 ±25	365 ±18	NS	
		Verbal fluency (total words)	Total Words	35.0 ±5.8	36.7 ±5.4	NS	
		BVRT	Correct	7.1 ±0.9	7.1 ±0.7	NS	

Reference	Year	Test	Scale	CPAP	Control	p =	Summary
Engleman et al.(104)	1998	SteerClear	Hits	63 (27)	71 (40)	NS	No changes reported.
		Trail making test	Part B	69 (32)	68 (32)	NS	
		Digit symbol substitution		52 (13)	52 (14)	NS	
		Block design		33 (9)	31 (8)	NS	
		Performance IQ decrement		3 (11)	4 (11)	NS	
		RVIP×	Correct	34 (15)	35 (13)	NS	
		8-choice reaction time	Ms	327 (46)	325 (38)	NS	
		2 second PASAT		37 (11)	35 (11)	NS	
		Verbal fluency	Total	41 (12)	42 (11)	NS	
		BVRT	correct	7.7 (1.5)	7.7 (1.7)	NS	
		NHP¥	Pt	7.0 (3.6)	7.0 (4.5)	NS	
Engleman et al.(103)	1999	SteerClear		189 ±156	195 ±158	NS	Improvements Reported CPAP: Digit Symbol Substitution Task; PASAT Subjects with mild AHI (5 to 10) experienced improved cognitive function
		Trail making test	Part A	26 ±11	29 ±11	NS	
		Trail making test	Part B	63 ±33	65 ±27	NS	
		Digit Symbol		59 ±12	57 ±14	0.004	
		Block Design Score		31 ±12	32 ±10	NS	
		Performance IQ Score		109 ±18	108 ±19	NS	
		PASAT 2-s	Correct	40 ±11	36 ±14	0.02	
Engleman et al.(173)	1994	Trail making test	Part B	66 (5)	75 (5)	0.02	Improvements Reported CPAP: • Vigilance • Mental flexibility • Attention
		Digit Symbol substitution		52 (2)	51 (2)	0.05	
		SteerClear		76 (5)	81 (6)	0.01	
		IQ decrement score		4.0 (2.1)	7.2 (2.0)	0.04	
Lojander et al.(183)	1999	BVRT	Correct,	1	-2	NR	Cognitive function did not correlate with daytime sleepiness or severity of OSAS. Success in treatment did not affect neuropsychologic outcome.
			Errors	-1	0		
			No. delayed	0	0		
		B –W^	Marked	-25	-4		
			Errors	1	0		
		Memory-Distractor task		0	0		
		Finger-Tapping Test		-3	-1		
		Trail making test	Part B	-19	-8		
		WAIS∆	VIQ	-7	-6		
			PIQ	-9	-5		
		WMS MQ∩		-7	-2		

Reference	Year	Test	Scale	CPAP	Control	p =	Summary
Monasterio et al.(187)	2001	WAIS	Digit symbol	9 (3)	9 (2)	0.97	No improvements reported
		WAIS	Digits forward and backward	11 (3)	11 (2)	0.56	
		Mental control		51 (27)	53 (27)	0.08	
		WMS^^	Verbal paired associated	41 (30)	43 (32)	0.63	
		Visual memory		61 (24)	63 (25)	0.06	
		Verbal fluency		69 (27)	70 (29)	0.53	
		WAIS	Block design	11 (3)	11 (3)	0.82	
		Trail making test	Part A	49 (19)	49 (20)	0.76	
			Part B	106 (42)	100 (39)	0.15	
		PASAT	4	14 (4)	16 (4)	020	
			3	15 (4)	15 (4)	0.20	
			2	12 (4)	12 (4)	0.12	
			1	5 (4)	5 (3)	0.32	
		SteerClear		8 (9)	8 (10)	0.88	
Woodson et al.(199)	2003	SRT Ω	Change	0.18 ±0.60	0.05 ±0.66	0.11	CPAP: nonsignificant improvement in simple reaction time
		RT∂	Change	-3.1 ±27.6	4.4 ±22.6	0.26	
		FRT⌂	Change	-0.8 ±13.0	-3.1 ±16.7	0.82	

AHI = Apnea-hypopnea index; BVRT = Benton visual retention test; CPAP = Continuous positive airway pressure; CWAT = Controlled word association task; FRT = Fastest reaction time; MAS = Mandibular advancement series; NHP = Neutral head position; NR = Not reported; NS = Not significant; OSAS = Obstructive sleep apnea syndrome; PASAT = Paced auditory test; PIQ = Performance intelligence test; PVT = Psychomotor vigilance test; RT = Reaction time; RVIPT = Rapid visual information processing task; SRT = Slowest reaction time; VIQ = Verbal intelligence quotient; WAIS = Wechsler adult intelligence scale; WMS MQ = Wechsler memory scale memory quotient.

No quantitative analyses of the data included in the table above were performed. This is because the wide variety of cognitive tests used in the studies included in the evidence base examine multiple cognitive domains and may test different aspects of each domain. Therefore, assembling them into broader categories may reduce only a small part of the variability inherent in any effort to group somewhat different articles into a single defined entity. Also, no single cognitive or psychomotor test was utilized in more than 50% of the included studies—we did not have a large enough evidence base to satisfy ECRI Institute requirements for meta-analysis. The findings of the 11 included studies are summarized in the following paragraph, followed by a more in-depth, study-by-study examination.

Overall, the findings regarding the effect of CPAP therapy on cognitive and psychomotor function were equivocal. Five studies(99,104,183,187,199) found no significant changes in cognitive and psychomotor function associated with CPAP use. Six studies(98,103,105,165,166,173) found the following results in cognitive and psychomotor function: improvement in overall cognitive function (k = 2); increased vigilance (k = 3); improvement in executive cognitive function (k = 2); improvement in verbal fluency (k = 1); improvement in mental flexibility (k = 2); and improvement in attention (k = 1).

Impact of CPAP on Measures of Daytime Sleepiness

Daytime sleepiness was assessed using three separate methods: subjectively using the ESS and objectively using the MSLT and the MWT. We present the findings of the included studies separately for each of these three measures.

Impact of CPAP on Subjective Daytime Sleepiness as Measured using the ESS

Fifteen included studies (Quality Rating: Moderate) reported on the effects of CPAP on ESS scores. The findings of these studies are summarized in Table 66.

Table 66. Impact of CPAP on Daytime Sleepiness (ESS)

Reference	Year	FUT	TG size (n =)	TG Mean (SD)	CG size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
Ballester et al.(164)	1999	3 months	68	5.6 (4.1)	37	10.6 (6.0)	-5.0 (-6.961, -3.309)	0.000
Barbe et al.(99)	2001	6 weeks	29	8.0 (3.2)	25	8.0 (5.0)	0.0 (-2.216, 2.216)	1.000
Barnes et al.(166)	2002	8 weeks	81	9.2 (3.7)	90	10.2 (3.7)	-1.0 (-2.136, 0.136)	0.084
Becker et al.(167)	2003	9 weeks	16	5.1 (3.8)	16	8.9 (5.0)	-3.8 (-6.877, -0.723)	0.016
Chakravorty et al.(170)	2002	3 months	32	8.0 (6.4)	21	11.0 (5.0)	-3.0 (-6.242, 0.242)	0.070
Coughlin et al.(171)	2007	6 weeks	34	9.4 (5.2)	34	12.5 (5.2)	3.1 (-5.594, -0.606)	0.015
Hack et al.(162)	1999	4 weeks	26	5.5 (2.2)	31	13.0 (10.6)	-7.5 (-11.678, -3.322)	0.000
Henke et al.(177)	2000	2 weeks	27	11.0 (5.2)	18	15.0 (7.7)	-4.0 (-7.803, -0.197)	0.039
Hui et al.(179)	2006	12 weeks	23	10.2 (4.7)	23	11.2 (5.2)	-1.0 (-3.913, 1.913)	0.501
Jenkinson et al.(180)	1999	4 weeks	52	7.0 (6.6)	49	13.0 (10.9)	-6.0 (-9.511, -2.489)	0.001
Loredo et al.(184)	2006	2 weeks	22	8.2 (4.4)	19	10.0 (4.5)	-1.8 (-4.529, 0.929)	0.196
Mansfield et al.(185)	2004	3 months	19	6.9 (4.3)	21	9.9 (4.5)	-3.0 (-5.778, -0.222)	0.034
Monasterio et al.(187)	2001	3 months	66	9.6 (5.5)	59	11.8 (5.2)	-2.2 (-4.082, -0.318)	0.022
Montserrat(188)	2001	6 weeks	23	6.6 (3.2)	22	14.5 (5.0)	-7.9 (-10.418, -5.462)	0.000
Pepperell et al.(193)	2002	4 weeks	53	6.8 (4.8)	51	11.3 (5.5)	-4.5 (-6.482, -2.518)	0.000

CG = Control group; FUT = Follow-up time; SD = Standard deviation; TG = Treatment group; WMD = Weighted mean difference.

Homogeneity testing of the data presented in the table above found that the findings of the 15 studies were heterogeneous ($q = 51.23$, $p < 0.0001$; $I^2 = 72.67$). Consequently, we were precluded from combining the data from these studies in a fixed-effects meta-analysis in order to obtain a single-point estimate of the CPAP impact on daytime sleepiness as measured by the ESS.

In an attempt to explain this heterogeneity, we performed a series of univariate meta-regression analyses. This was because the development of multivariate models was precluded by the small size of the evidence base. The covariates considered in this analysis, which were chosen *a priori*, and the findings of each regression are presented in Table 67.

Table 67. Findings – CPAP and Daytime Sleepiness Univariate Meta-regression Analyses (unrestricted maximum likelihood model)

Covariate	Coefficient	95% CI	p =	Coefficient significant?	Residual	Model	Total	Tau²
Patient Level Covariates								
BMI	0.15184	-0.48 to 0.11	0.22050	No	q = 14.92440 p = 0.31210	q = 1.50114 p = 0.22050	q = 16.42555 p = 0.28808	2.68568
Age	0.18215	-0.55 to 0.17	0.30066	No	q = 15,17272 p = 0.29669	q = 1.07125 p = 0.30066	q = 16.24397 p = 0.29870	2.73431
AHI/Severity	NC	NC	NC	NC	NC	NC	NC	NC
Study Level Covariates								
Time Studied	NC	NC	NC	NC	NC	NC	NC	NC

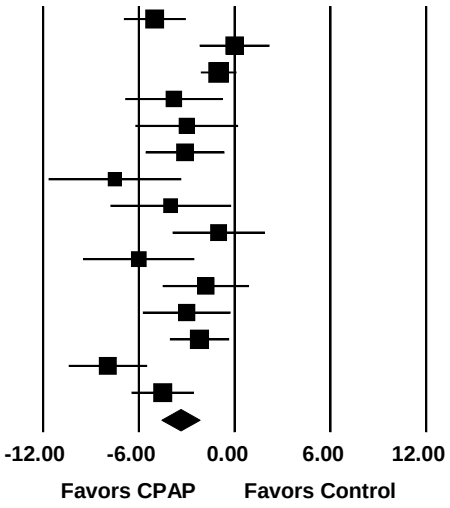
AHI = Apnea-hypopnea index; BMI = Body mass index; NC = Not calculated because necessary data were not reported by all included studies.

Our meta-regression analyses found that none of the covariates examined were significantly correlated with ESS score, and heterogeneity could not be explained. The unexplained quantitative inconsistency in these data precludes one from determining a single estimate of the effect of CPAP on subjective daytime sleepiness.

In order to obtain an estimate of the overall impact of CPAP on subjective daytime sleepiness, we pooled the data from each the 10 included studies using random-effects meta-analysis. The findings of this more conservative analysis, which are presented in Figure 41, indicate that, on average, CPAP significantly reduces daytime sleepiness scores by approximately 3.415 (CI 95%: 4.61, 2.21) units. A series of sensitivity analyses (Appendix H) found these findings to be robust.

Figure 41. Impact of CPAP on Daytime Sleepiness as Defined by ESS

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Ballester	-5.000	1.001	1.001	-6.961	-3.039	-4.997	0.000
Barbe	0.000	1.131	1.278	-2.216	2.216	0.000	1.000
Barnes	-1.000	0.580	0.336	-2.136	0.136	-1.725	0.084
Becker	-3.800	1.570	2.465	-6.877	-0.723	-2.420	0.016
Chakravorty	-3.000	1.654	2.737	-6.242	0.242	-1.813	0.070
Coughlin	-3.100	1.273	1.619	-5.594	-0.606	-2.436	0.015
Hack	-7.500	2.132	4.545	-11.678	-3.322	-3.518	0.000
Henke	-4.000	1.940	3.765	-7.803	-0.197	-2.061	0.039
Hui	-1.000	1.486	2.209	-3.913	1.913	-0.673	0.501
Jenkinson	-6.000	1.791	3.208	-9.511	-2.489	-3.350	0.001
Loredo	-1.800	1.393	1.939	-4.529	0.929	-1.293	0.196
Mansfield	-3.000	1.418	2.010	-5.778	-0.222	-2.116	0.034
Monasterio	-2.200	0.960	0.922	-4.082	-0.318	-2.291	0.022
Montserrat	-7.940	1.264	1.598	-10.418	-5.462	-6.281	0.000
Pepperell	-4.500	1.011	1.022	-6.482	-2.518	-4.450	0.000
	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000



Meta Analysis

A subset of randomized crossover studies did not report the results of the first arm of the research and were not included in the analysis above. The findings of these four studies are summarized in Table 68.

Table 68. Impact of CPAP on Daytime Sleepiness (ESS) (Single-arm studies)

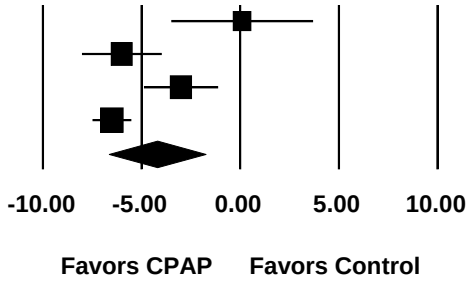
Reference	Year	FUT	TG size (n =)	TG Mean (SD)	CG size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
McArdle et al.(186)	2001	12 months	23	6.0 (0.6)	23	12.5 (2.3)	-6.500 (-7.508, -5.492)	0.000
Engleman et al.(104)	1998	8 weeks	23	6.0 (3.0)	23	12.0 (4.0)	-6.000 (-8.043, -3.957)	0.000
Engleman et al.(103)	1999	8 weeks	34	8.0 (4.0)	34	11.0 (4.0)	-3.000 (-4.901, -1.099)	0.002
Engleman et al.(92)	1996	2 – 6 months	16	10.1 (5.6)	16	10.0 (4.0)	0.100 (-3.514, 3.714)	0.957

CG = Control group; FUT = Follow-up time; SD = Standard deviation; TG = Treatment group; WMD = Weighted mean difference.

Homogeneity testing found that the findings of the five studies differed from one another by a greater degree than one would expect by chance alone (q = 31.04, p <0.0001: I2 = 87.11). Consequently, we were precluded from combining the data from these studies in a fixed-effects meta-analysis in order to obtain a single estimate of the CPAP effects on daytime sleepiness as measured by the ESS (Figure 42).

Figure 42. REMA – Impact of CPAP on Daytime Sleepiness as Defined by ESS (single-arm studies)

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Engleman 1	0.100	1.844	3.400	-3.514	3.714	0.054	0.957
Engleman 2	-6.000	1.043	1.087	-8.043	-3.957	-5.755	0.000
Engleman 3	-3.000	0.970	0.941	-4.901	-1.099	-3.092	0.002
McArdle	-6.500	0.514	0.265	-7.508	-5.492	-12.638	0.000
	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001

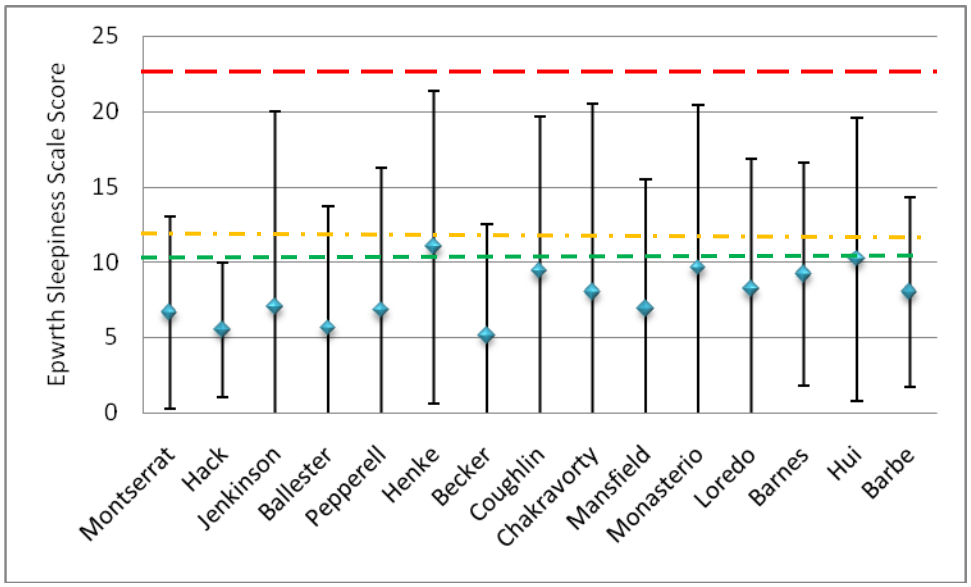


Meta Analysis

Pooling these data using random-effects meta-analysis found that CPAP reduced objective daytime sleepiness as measured using the ESS scores by an average of 4.228 (CI 95%: -1.77, -6.68) units. These findings are consistent with the findings of the previous findings. A series of sensitivity analyses found the findings of this meta-analysis to be robust.

Although the available evidence suggests that CPAP improves the ESS score, the findings above do not tell us whether CPAP is so effective that it improves the ESS score to normal levels. Figure 43 shows the mean ESS score and 95% confidence intervals of the enrollees in each of the 15 included studies at final follow-up. It can be seen that while CPAP may be effective, some individuals will still experience daytime sleepiness.

Figure 43. Impact of CPAP on ESS Score at Final Follow-up



Key:
Green: Normal range, upper limit, 0 – 10
Yellow: Borderline sleepy, upper limit, 10-12
Red: Abnormal, upper limit, 12 - 24

Impact of CPAP on Objective Daytime Sleepiness as Measured using the MSLT

Three included studies (Quality Rating: Moderate) reported on the effects of CPAP on daytime sleepiness (as identified by the MSLT) associated with OSA. The findings of these studies are summarized in Table 61.

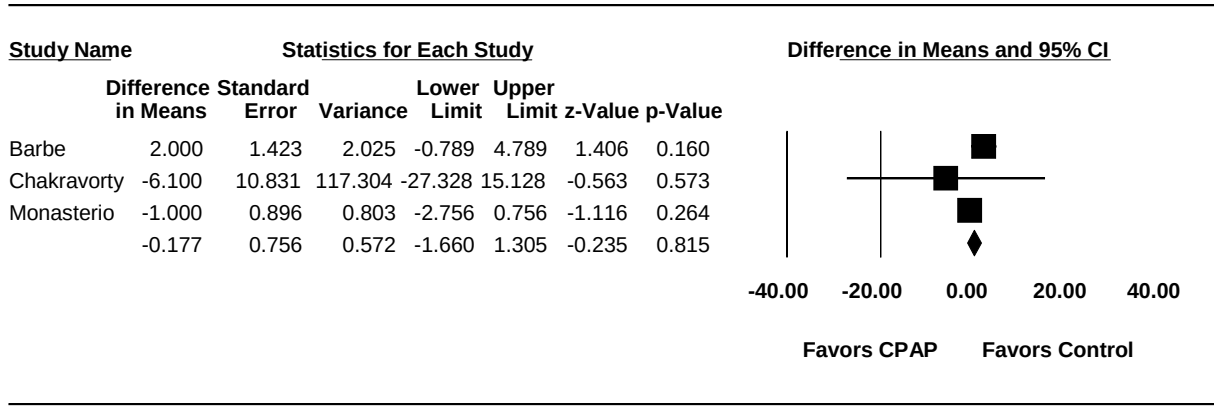
Table 69. Impact of CPAP on Daytime Sleepiness (MSLT)

Reference	Year	FUT	TG size (n =)	TG Mean (SD)	CG size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
Barbe et al.(99)	2001	6 weeks	29	13 (5.39)	25	11 (5.0)	2.000 (-0.789, 4.789)	0.160
Chakravorty et al.(170)	2002	3 months	32	33.9 (38.8)	21	40 (38.2)	-6.100 (-27.328, 15.128)	0.573
Monasterio et al.(187)	2001	3 months	66	10 (5.0)	59	11 (5.0)	-1.000 (-2.756; 0.756)	0.573

CG = Control group; FUT = Follow-up time; SD = Standard deviation; TG = Treatment group; WMD = Weighted mean difference.

A test of homogeneity found that the findings of the three studies were not significantly different from one another (q = 3.484, p <0.0001; I2 = 42.594). Consequently, we combined the data into a fixed-effects meta-analysis in order to obtain a single-point estimate of the effect of CPAP on daytime sleepiness (Figure 44).

Figure 44. FEMA – Effect of CPAP on Daytime Sleepiness as defined by MSLT



The results of this meta-analysis do not provide evidence to support the contention that CPAP decreases daytime sleepiness levels when this outcome is measured objectively as 0.77 (CI 95%: -1.660 to 0.572, p = 0.815) units.

Impact of CPAP on SaO_2

Eight included studies (Quality Rating: Moderate) reported on the effects of CPAP on SaO_2 associated with OSA. The findings of these studies are summarized in Table 70.

Table 70. Impact of CPAP on SaO_2

Reference	Year	Outcome Assessed	FUT	TG Size (n =)	TG Mean (SD)	CG Size (n =)	CG Mean (SD)	WMD (95% CI)	*p* =
Hui et al.(179)	2006	Oxygen Saturation	12 weeks	23	75.6 (13.4)	23	75.1 (15.3)	0.500 (-7.834, 8.834)	0.906
Norman et al.(189)	2006	Oxygen Saturation	2 weeks	18	93.6 (3.1)	15	90.1 (3.0)	3.500 (1.407, 5.593)	0.001
Ryan et al.(195)	2005	Oxygen Saturation	1 month	10	90.5 (3.4)	8	70.1 (13.8)	20.400 (11.539, 29.261)	0.000
Barnes et al.(166)	2004	Oxygen Saturation	12 weeks	89	91.9 (2.3)	90	85.4 (5.6)	6.500 (5.181, 7.819)	0.000
Mansfield et al.(185)	2004	Oxygen Saturation	3 months	19	91.1 (3.9)	21	77.2 (16.0)	13.900 (6.487, 21.313)	0.000
Becker et al.(167)	2003	Oxygen Saturation	9 weeks on average	16	80.5 (16.8)	16	72.0 (15.7)	8.500 (-2.767, 19.767)	0.139
Kaneko et al.(181)	2003	Oxygen Saturation	4 weeks	12	89.6 (3.8)	12	76.9 (12.4)	12.700 (5.323, 20.077)	0.000
Henke et al.(177)	2001	Oxygen Saturation	2 weeks on average	27	85.8 (8.4)	18	67.2 (17.7)	18.600 (10.904, 26.296)	0.000

CG = Control group; FUT = Follow-up time; SD = Standard deviation; TG = Treatment group; WMD = Weighted mean difference.

A formal assessment of the data presented above for quantitative consistency (homogeneity testing) found the findings of the eight studies to be heterogeneous ($Q = 35.42$; $p < 0.0001$; $I^2 = 80.24$). Because we do not perform meta-regression to investigate heterogeneity when there are fewer than 10 studies per covariate, the source of the heterogeneity in this evidence base was not established. Consequently, we were precluded from combining the data into a fixed-effects meta-analysis.

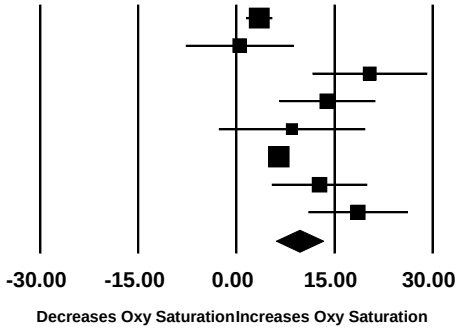
Pooling of these data using a random-effects meta-analysis (found that, on average, CPAP increased SaO_2 levels by 9% (CI 95%: 5.96%, 13.19%). A series of sensitivity analyses found these findings to be robust. Thus, we can be reasonably confident that CPAP has a positive impact on SaO_2 levels. Because of the presence of unexplained heterogeneity, however, we are precluded from providing a precise estimate of the magnitude of this improvement. Our best estimate at this time is that CPAP improves SaO_2 in the average individual with moderate-to-severe OSA by approximately 6% to 13%.

Figure 45. REMA - CPAP and SaO_2

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limi	z-Value	p-Value
Norman	3.500	1.068	1.141	1.407	5.593	3.277	0.001
Hui	0.500	4.252	18.079	-7.834	8.834	0.118	0.906
Ryan	20.400	4.521	20.438	11.539	29.261	4.512	0.000
Mansfield	13.900	3.782	14.304	6.487	21.313	3.675	0.000
Becker	8.500	5.749	33.046	-2.767	19.767	1.479	0.139
Barnes	6.500	0.673	0.453	5.181	7.819	9.657	0.000
Kaneko	12.700	3.764	14.168	5.323	20.077	3.374	0.001
Henke	18.600	3.927	15.419	10.904	26.296	4.737	0.000
	9.582	1.846	3.406	5.964	13.199	5.192	0.000

Statistics for each study

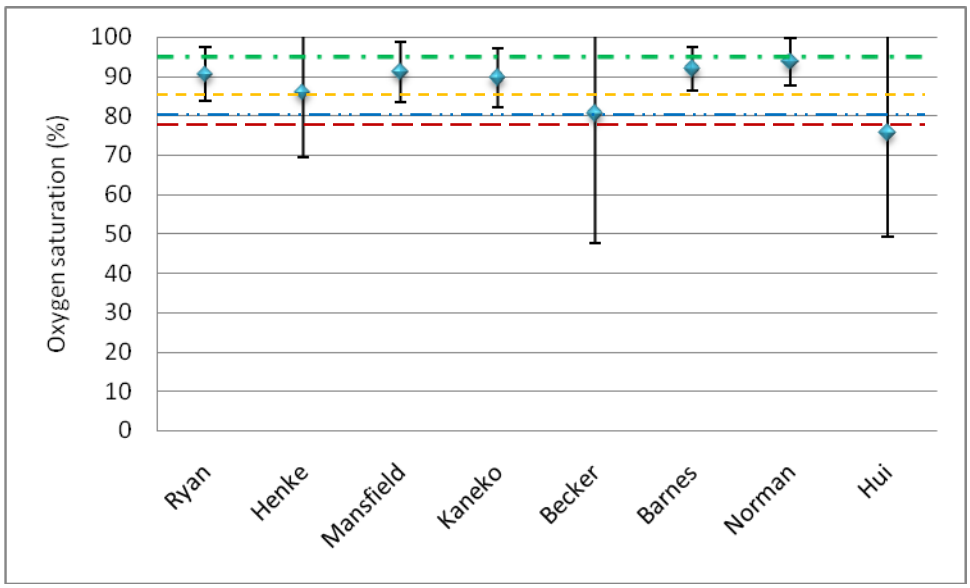
Difference in Means and 95% CI



Meta Analysis

Although the available evidence suggests that CPAP increases blood SaO_2, the findings above do not tell us whether CPAP is so effective that it improves SaO_2 to normal levels. Figure 46 shows the mean SaO_2 and 95% confidence intervals for the enrollees in each of the eight included studies at final follow-up. It can be seen that while CPAP may be effective, SaO_2 levels will remain suboptimal for many individuals.

Figure 46. Impact of CPAP on Blood SaO_2 Levels at Final Follow-up



Key:
Green: Normal SaO_2, lowest level, ≥95%
Yellow: Mild SaO_2 decrease, lowest level, 86%
Blue: Moderate SaO_2 decrease, lowest level, 80-85%
Red: Severe SaO_2 decrease, ≤79%

Dental Appliances and Indirect Measures of Driving Performance

A total of two studies examined for inclusion in the evidence base for Key Question 5 reported on the effect of dental appliances on indirect measures of driving performance. The primary attributes of these two studies are presented in Table 71.

Table 71. Primary Attributes of Included Studies that Examined the Impact of Dental Appliances

Reference	Year	Study Design	Method of Diagnosis	Prospective or Retrospective	Comparison of Interest	Study Population	Was compliance assessed?
Barnes et al.(166)	2004	RCT – Crossover	PSG	Prospective	CPAP vs. MAS vs. Placebo	n = 80 Individuals referred for investigation of sleep-disordered breathing	57% CPAP 29% MAS (self-reported)
Hoekema et al.(155)	2006	RCT	PSG	Prospective	CPAP vs. Oral Appliance vs. Control	n = 36 Individuals aged 21-70	100% compliance

CPAP = Continuous positive airway pressure; MAS = Mandibular advancement series; PSG = Polysomnogram; RCT = Randomized controlled trial.

Quality of Studies that Examined the Effects of Dental Appliances on Indirect Measures of Driving Performance

The overall quality of the studies included in this subsection of the report is moderate. One of the studies was an RCT; the second included study was a randomized controlled crossover trial. Both studies were of moderate quality. Information about this quality assessment is included in Table 72.

Table 72. Quality of Included Studies that Examined the Impact of Dental Appliances

Reference	Year	Instrument Used	Score	Quality
Barnes et al.(166)	2004	ECRI Institute Quality Assessment Scale I: Randomized and Nonrandomized studies	5.0	Moderate
Hoekema et al.(155)	2006	ECRI Institute Quality Assessment Scale I: Randomized and Nonrandomized studies	5.7	Moderate

Generalizability of Evidence to the Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 5: Part C are similar to CMV drivers in the United States. In general, the populations in these studies contain >50% males between the ages of 35 and 60, which may present some similarities to the population predominantly found among CMV drivers in the United States. However, we can only ascertain from one of these studies(155) the extent of driving exposure in the participants, or whether any of them were professional drivers. Thus, our ability to generalize beyond factors such as age or gender is limited. Other important characteristics of the individuals included in the studies that address Key Question 5: Part C are presented in Table 73.

Table 73. Generalizability of Included Studies that Examined the Impact of Dental Appliances

Reference	Year	Type of Sleep Apnea	Mean Age	AHI (Mean, SD)	% Male	Driving Exposure	% CMV Drivers	Generalizability to Target Population
Barnes et al.(166)	2004	OSA	46.4 ±1.1 years	21.3 ±1.3	80	NR	NR	Unknown
Hoekema et al.(155)	2006	OSA	Oral appliance 48.7 ±11.2 Control 48.7 ±10.0	OSAHS patients (CPAP + Oral Appliance) 49.1 ±33.3	OSAHS patients 85 Control 82	OSAHS patients 29 ±10 years of driving experience 15 (10-32) annual number of kilometers x 10^3 Control 29 ±11 years of driving experience 13 (6-20) annual number of kilometers x 10^3	NR	Unknown

AHI = Apnea-hypopnea index; CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; NR = Not reported; OSAHS = Obstructive sleep apnea-hypopnea syndrome; NR = Not reported; SD = Standard deviation.

Findings of Studies that Assessed Impact of Dental Appliances

Indirect Measures Assessed

The purpose of this subsection is to provide details of the indirect measures assessed in the studies included in the Dental Appliance evidence base. The indirect measures assessed by the two included studies are presented in Table 74. They include AHI (k = 2), daytime sleepiness (k = 2), cognitive and psychomotor function (k = 2), SaO_2 (k = 2), and blood pressure (k = 1).

Table 74. Indirect Measures Assessed by Included Studies that Examined the Impact of Dental Appliances

Reference	Year	AHI	Daytime sleepiness	Cognitive and Psychomotor Function	Oxygen Saturation	Blood Pressure
Barnes et al.(166)	2004	✓	✓	✓	✓	✓
Hoekema et al.(155)	2006	✓	✓	✓	✓	
Totals		**2**	**2**	**2**	**2**	**1**

AHI = Apnea-hypopnea index.

Impact of Dental Appliance Use on AHI

Barnes et al.(166) (Quality Rating: Moderate) compared the efficacy of an oral appliance (the mandibular advancement splint, or MAS) to a placebo and to CPAP in the treatment of OSA. This trial demonstrated that both MAS and CPAP significantly improved AHI ($p < 0.001$) when compared to baseline and placebo therapy. In particular, MAS improved SDB by 49.1% for individuals who demonstrated a complete response (defined as a reduction in AHI events to below 10/hour), and a further 6.1% in individuals who demonstrated a partial response (defined as a reduction of AHI events by 50% but not below 10). Limitations to this study included the self-reporting of MAS use versus the objective reporting of CPAP use and a dropout rate of 30%, which occurred primarily among individuals with mild OSA. This situation may have then introduced a bias that would increase the magnitude of the treatment response as the attrition level rose.

Hoekema et al.(155) (Quality Rating: Moderate) compared the effect of CPAP and oral appliances used in the treatment of OSA in a study on simulated driving performance: AHI functioned as an outcome of interest. The authors found that AHI improved in both the oral appliance group ($p = 0.008$ for difference between baseline and within treatment group follow-up) and in the CPAP group ($p = 0.001$ for difference between baseline and within treatment group follow-up), and that the difference in responses between the two groups was not significant at final follow-up. Potential limitations to this study include selection bias (choosing controls from among hospital employees); essential differences in the baseline values for OSA among those randomized to the CPAP group; and questions regarding whether adequate statistical power was attained.

Impact of Dental Appliance Use on Blood Pressure

Barnes et al.(166) (Quality Rating: Moderate) compared the efficacy of an oral appliance (the MAS) to a placebo and to CPAP in the treatment of OSA. This RCT demonstrated no statistically significant changes in either systolic or diastolic blood pressure levels in the MAS group. While nocturnal and diurnal blood pressure is not featured in this report, it should be noted that Barnes et al. found an small improvement in nocturnal diastolic blood pressure (baseline 69.4 [SEM 0.9], 67.2 [SEM: 0.8], which was considered statistically significant at $p < 0.05$ (CPAP versus MAS), $p < 0.01$ (baseline versus MAS) and $p < 0.05$ (placebo versus MAS).

Impact of Dental Appliance Use on Measures of Daytime Sleepiness

Barnes et al.(166) (Quality Rating: Moderate) compared the efficacy of an oral appliance (the MAS) with a placebo and to CPAP in the treatment of OSA. The trial demonstrated improvements in subjective daytime sleepiness (ESS scores) with both CPAP and MAS therapy. In the CPAP group, mean ESS levels fell to 9.2 (SEM: 0.4; $p < 0.001$ compared to baseline; $p < 0.001$ compared to placebo); in the MAS group, mean ESS levels fell to levels identical to those found in the CPAP group. Objective daytime sleepiness was established utilizing the MWT[17].(200) At baseline, the individuals in the study recorded an average MWT score of 30.7 (SEM: 0.9), with a total of 18.4% having an MWT score that would qualify for the pathologically sleepy category. With treatment, the CPAP group recorded an average MWT score of 30.0 (SEM: 0.9), while the MAS group recorded an average MWT score of 29.6 (SEM: 0.9). From this data the authors concluded that objective sleepiness as determined by MWT scores did not improve with MAS therapy.

[17] MWT scoring: in a 20 minute test, an individual who is not sleepy will typically have a mean latency score of 18.7 minutes. An individual with pathological sleepiness will typically have a mean latency score of <11 minutes.

Hoekema et al.(155) (Quality Rating: Moderate) compared the effect of CPAP and oral appliances used in the treatment of OSA in a study on simulated driving performance: daytime sleepiness (ESS) functioned as an outcome of interest. The authors concluded that subjective daytime sleepiness improved only in the CPAP group. Upon reviewing the final data, it was found that there were no significant differences in ESS between the CPAP and oral appliance groups.

Impact of Dental Appliances on SaO_2

Barnes et al.(166)(Quality Rating: Moderate) studied the treatment comparison of CPAP to an MAS and placebo tablet for patients with mild to moderate OSA. The predominately male (80%) patient population with baseline scores for minimum SaO_2 (%) (86.7 ±0.6) demonstrated statistically significant changes in saturation levels in CPAP and MAS versus placebo ($p < 0.001$) and CPAP versus baseline ($p < 0.001$). Investigators concluded that MAS and CPAP can improve SaO_2 levels; however, a greater treatment response was demonstrated with use of CPAP.

Hoekema et al.(155)(Quality Rating: Moderate) investigated the treatment effects of an oral appliance (OA) versus CPAP on simulated driving performance of OSA patients. As a result of both treatments, minimum SaO_2 improved significantly when compared to baseline values (OA; $p = 0.01$, CPAP; $p = 0.007$).

Pharmacotherapy and Indirect Measures of Driving Performance

A total of eight included studies reported on the impact of pharmacotherapy and at least one indirect measure of driving performance. The primary attributes of these eight studies are presented in Table 75. Three studies examined the impact of theophylline, three examined the impact of modafinil or armodafinil, one study looked at mirtazapine, and the remaining study assessed the impact of salmeterol.

Table 75. Primary Attributes of Included Studies that Examined the Impact of Pharmacotherapy

Reference	Year	Study Design	Method of Diagnosis	Prospective or Retrospective	Comparison of Interest	Study Population	Was compliance assessed?
Carley et al.(169)	2007	RCT – Crossover	PSG	Prospective	Mirtzapine 4.5 mg/15 mg vs. placebo	n = 12 Treatment naïve, newly diagnosed adults	NR
Hein et al.(176)	2000	RCT - Crossover	PSG	Prospective	Theophylline vs. placebo	n = 14 Individuals using home-monitoring equipment	NR
Hirshkowitz et al.(178)	2007	RCT	PSG	Prospective	Armodaphinil + CPAP vs. Placebo + CPAP	n = 259 Individuals with OSA from 36 study sites internationally	NR
Kingshott et al.(100)	2001	RCT - Crossover	Previously diagnosed	Prospective	Modafinil+CPAP vs. Placebo+CPAP	n = 30 Individuals attending single sleep clinic	Modafinil: 99.3 ±2.7 Placebo: 97.3 ±5.2
Oberndorfer et al.(190)	2000	RCT - Crossover	PSG	Prospective	Theophylline vs. placebo	n = 30 Individuals diagnosed with OSA	NR
Orth et al.(201)	2005	RCT - Crossover	PSG	Prospective	Theophylline+CPAP vs. Placebo+CPAP	n = 16 Individuals with mild-moderate OSA	NR
Pack et al.(101)	2001	RCT	Previously diagnosed	Prospective	Modafinil+CPAP vs. Placebo+CPAP	n = 157 Individuals with CPAP-resistant daytime sleepiness	NR
Rasche et al.(194)	1999	RCT - Crossover	PSG	Prospective	Salmeterol vs. placebo	n = 20 All with OSA	NR

CPAP = Continuous positive airway pressure; NR = Not reported; OSA = Obstructive sleep apnea; PSG = Polysomnogram; RCT = Randomized controlled trial.

Quality of Studies that Examined the Effects of Pharmacotherapy on Indirect Measures of Driving Performance

The purpose of this subsection is to provide details regarding the quality of the included studies that address Key Question 5: Part C. Six of the studies were randomized controlled crossover trials, with five having a moderate-quality rating and one having a high-quality rating. The remaining two studies were RCTs, each with a high-quality rating. Information about this quality assessment is included in Table 76. As demonstrated, the overall quality of the included studies was moderate (7.4)

Table 76. Quality of Included Studies that Examined the Impact of Pharmacotherapy

Reference	Year	Instrument used	Quality
Carley et al.(169)	2007	ECRI Institute Quality Assessment Scale I	Moderate
Hein et al.(176)	2000	ECRI Institute Quality Assessment Scale I	Moderate
Hirshkowitz et al.(178)	2007	ECRI Institute Quality Assessment Scale I	High
Kingshott et al.(100)	2001	ECRI Institute Quality Assessment Scale I	Moderate
Oberndorfer et al.(190)	2000	ECRI Institute Quality Assessment Scale I	Moderate
Orth et al.(201)	2005	ECRI Institute Quality Assessment Scale I	High
Pack et al.(101)	2001	ECRI Institute Quality Assessment Scale I	Moderate
Rasche et al.(194)	1999	ECRI Institute Quality Assessment Scale I	High

Generalizability of Evidence to the Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 5: Part C are similar to CMV drivers in the United States. In general, the populations in these studies contain >50% males between the ages of 20 and 67, which may present some similarities to the population predominantly found among CMV drivers in the United States. However, we cannot ascertain from these studies the extent of driving exposure in the participants, or whether any of them were professional drivers. Thus, our ability to generalize beyond factors such as age or gender is limited. Other important characteristics of the individuals included in the studies that address Key Question 5: Part C are presented in Table 77.

Table 77. Generalizability of Included Studies that Examined the Impact of Pharmacotherapy

Reference	Year	Type of Sleep Apnea	Mean Age	AHI (Mean, SD)	% Male	Driving Exposure	% CMV Drivers	Generalizability to target population
Carley et al.(169)	2007	OSA	Men 39.0 ±18.3 Women 43.4 ±14.2	Placebo: 22.3 ±16.6 Mirtazapine 4.5mg: 13.5 ±12.81 Mirtazapine 15mg: 11.4 ±12.47	58%	NR	NR	Unknown
Hein et al.(176)	2000	OSA	50 ±8	13.8 ±4.0 (at PSG)	86%	NR	NR	Unknown
Hirshkowitz et al.(178)	2007	OSA	Armodafinil: 50.7 ±9.2 Placebo: 50.6 ±8.9	During CPAP: Armodafinil:1.1 ±2.1 Placebo: 1.4 ±2.3	Armodafinil: 75% Placebo: 92%	NR	NR	Unknown
Kingshott et al.(100)	2001	NR	53 ±7	45 ±31	90%	NR	NR	Unknown
Oberndorfer et al.(190)	2000	Moderate OSA	55.5 ±9.3	Median & 25/75% Baseline: 9 (5.6/24.2) Placebo: 13.2 (9.8/20.2) Theophylline: 6.3 (5.7/9/1)	91%	NR	NR	Unknown
Orth et al.(201)	2005	OSA	56.9 ±9.7	Baseline: 37.9 ±17.9 CPAP: 7.9 ±6.4 CPAP + Placebo: 4.5 ±3.7 CPAP + theophylline: 4.3 ±3.3	100%	NR	NR	Unknown
Pack et al.(101)	2001	OSA	Modafinil + CPAP 50 (32 - 76) Placebo + CPAP 50 (28 - 72)	RDI events: Placebo: 46.8 ±33.7 Modafinil: 53.7 ±30	Placebo: 74% Modafinil: 79%	NR	NR	Unknown
Rasche et al.(194)	1999	OSA	53.0 ±7.8	Baseline: 35.6 ±25.3 Placebo: 27.7 ±16.8 Salmeterol: 31.8 ±17.8	80%	NR	NR	Unknown

AHI = Apnea-hypopnea index; CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; OSA = Obstructive sleep apnea; RDI = Respiratory distress index; SD = Standard deviation.

Findings of Studies that Assessed Impact of Pharmacotherapy

Indirect Measures Assessed

The purpose of this subsection is to provide details of the indirect measures assessed in the studies included in the Pharmacotherapy Evidence Base. Of the eight included studies, five assessed the influence of pharmacotherapy on AHI, four assessed the influence of pharmacotherapy on daytime sleepiness, four assessed the influence of pharmacotherapy on SaO_2, and two assessed the influence of pharmacotherapy on blood pressure among individuals with OSA. None of the studies assessed the influence of pharmacotherapy on cognitive and psychomotor function. The indirect measures assessed are featured in Table 78.

Table 78. Indirect Measures Assessed by Included Studies that Examined the Impact of Pharmacotherapy

Reference	Year	AHI	Daytime sleepiness	Cognitive and Psychomotor Function	Oxygen Saturation	Blood Pressure
Carley et al.(169)	2007	✓	✓		✓	✓
Hein et al.(176)	2000	✓			✓	
Hirshkowitz et al.(178)	2007		✓			
Kingshott et al.(100)	2001		✓			
Oberndorfer et al.(190)	2000	✓				
Orth et al.(201)	2005	✓			✓	
Pack et al.(101)	2001		✓			✓
Rasche et al.(194)	1999	✓			✓	
Totals		**5**	**4**	**0**	**4**	2

AHI = Apnea-hypopnea index.

Pharmacotherapy and AHI

By far, the largest number of included studies related to AHI can be found in the CPAP subsection of the evidence base. This subsection addresses the second largest AHI-centered evidence base, pharmacotherapy.

Mirtazapine

Carley et al.(169) (Quality Rating: Moderate) attempted to determine whether the antidepressant mirtazapine would reduce AHI in individuals with OSA. The RCT of 12 individuals with OSA with varying degrees of severity found that 4.5 mg daily doses of mirtazapine were associated with a decrease in AHI from placebo treatment levels of 22.3 events per hour to 13.5 AHI events per hour, or 52% of placebo level. Daily doses of 15 mg mirtazapine were associated with a decrease in AHI events from 22.3 (placebo level) to 11.4 events per hour, or 46% of placebo level. It was also noted that the size of the treatment effect was related to AHI severity as recorded at baseline (AHI during placebo treatment).

The authors discussed several important limitations to the study, including: the small sample size (n = 12); the short length of time allotted for treatment periods (7 days); and the lack of washout periods between treatments. In addition, they mentioned two side effects of mirtazapine that might impact the health of individuals with OSA, namely weight gain and sedation, and ultimately concluded that mirtazapine should not yet be considered a treatment for OSA.

Theophylline

Hein et al.(176)(Quality Score: Moderate) attempted to determine whether the bronchodilator theophylline would reduce AHI in individuals with OSA. The study found that theophylline therapy was associated with a decrease in AHI (7 day at-home monitoring period), with baseline 9.2 (SD: ±7.7) events per hour reduced to 6.7 (SD: ±6.1) AHI events per hour. The authors concluded that, while theophylline demonstrated a potential to influence AHI, this potential did not reach clinical significance.

Oberndorfer et al.(190) (Quality Score: Moderate) examined the effect of theophylline on sleep disorders of different severity, including primary snoring, obstructive snoring, and moderate sleep apnea. It was determined that AHI events decreased associated with theophylline therapy when compared to baseline and placebo information (baseline median and percentiles 25/75, 9.0 events per hour, [5.6/24.2]; placebo 13.2 events per hour [9.8/20.2]; and theophylline 6.3 events per hour [5.7/9.1]).

Orth et al.(201) (Quality Score: Moderate) examined the effectiveness of theophylline as an adjunct therapy to CPAP in improving ventilation for individuals with OSA. There was no change in the AHI with adjunctive theophylline therapy (placebo, 4.5 ±3.7 events per hour versus theophylline, 4.3 ±3.3 events per hour). The authors concluded that adjunctive theophylline therapy provided no reduction in AHI over the short term, but posited that long term use of theophylline may demonstrate some reductive effect on AHI.

Salmeterol

Rasche et al.(194) (Quality Score: Moderate) examined the efficacy and safety of the bronchodilator salmeterol (trade name: Serevent) as a therapeutic intervention for individuals with OSA. The researchers concluded that there were no differences in efficacy of salmeterol in treating OSA when compared to placebo (baseline AHI 35.6 events per hour [SD: 25.3], placebo AHI 27.7 events per hour [SD: 16.8], salmeterol AHI31.8 events per hour [SD: 17.8])

Pharmacotherapy and Daytime Sleepiness

Kingshott et al.(100) (Quality Score: Moderate) compared the efficacy of modafinil to a placebo as a therapeutic option for individuals with CPAP-resistant daytime sleepiness. In this randomized controlled crossover trial (n = 30), the primary outcome – daytime sleepiness – was examined using ESS (subjective); the secondary outcome measures were obtained using the MSLT and MWT. The authors concluded that subjective sleepiness as measured with the ESS, and objective sleepiness as measured by the MSLT, demonstrated no statistically significant improvement, while the MWT demonstrated an improvement in daytime sleepiness. Several explanations were posited for this difference in results; of particular note were the placebo effects detected with the ESS and MSLT, which potentially introduced a greater probability of finding therapy-related differences with the MWT. Kingshott et al. concluded that modafinil may be a useful adjunct therapy in a select population of CPAP users (those with resistant OSA), but would not be appropriate as a primary therapeutic option.

As with Kingshott et al. Pack et al.(101) (Quality Score: Moderate) investigated the efficacy of adjunctive modafinil therapy for CPAP-resistant daytime sleepiness. The authors concluded that there were statistically significant improvements in the ESS (subjective) and MSLT (objective) measures of daytime sleepiness in the CPAP/modafinil group when compared to the same measures of daytime sleepiness in the CPAP/placebo group. More individuals (51%) in the CPAP/modafinil group achieved normalized (<10) ESS scores than in the CPAP/placebo group (27%). Individuals with mild to moderate EDS (baseline ESS 10 – 14) experienced an improvement in ESS scores with the addition of modafinil, as did individuals with more severe daytime sleepiness (≥15 baseline ESS). Kingshott et al. mentioned two methodologic issues present in the study: the lack of a standardized definition of apnea and hypopnea across the study sites, and the potential for changes in CPAP compliance with the addition of modafinil therapy. Taking these considerations in mind, the authors ultimately concluded that modafinil may be an effective adjunct treatment for CPAP-resistant OSA with residual daytime sleepiness.

Hirshkowitz et al.(178) (Quality Score: High) investigated the efficacy of armodafinil as an adjunct therapy for CPAP-resistant daytime sleepiness (using the ESS and MWT tests), particularly in improving wakefulness and cognition, and in the reduction of fatigue. Post-therapeutic mean changes for MWT in the armodafinil group ranged from 1.5 – 2.2 minutes; in the placebo group the measures ranged from -0.1 – 0.6 minutes, for a $p > 0.05$. Post-therapeutic scores for the ESS were not reported in such as way that a figure can be given here. The authors noted two particular issues with this study: the relatively short treatment period, which may limit the usefulness of the results when considering long-term armodafinil therapy; and generalizability issues regarding the nature of the population, which consisted of individuals who were experiencing CPAP-resistant daytime sleepiness. Hirshkowitz et al. concluded that adjunctive armodafinil therapy improved the wakefulness and reduced fatigue in this select population of individuals with OSA who were CPAP-compliant.

Pharmacotherapy and SaO_2

Carley et al.(169) (Quality Score: Moderate) attempted to determine whether the antidepressant mirtazapine (trade name: Remeron®) would reduce AHI in individuals with OSA. Among the main outcomes examined in this study were AHI, SaO_2, and daytime sleepiness. There was a lack of effect by mirtazapine on SaO_2, which was attributed by the authors to "the fact that residual respiratory events were not shortened, and at least occasionally, were expressed in repetitive sequences such that the minimum SaO_2 was not improved." Several important limitations to the study were raised, including: the small sample size (n = 12); the short length of time allotted for treatment periods (7 days); and the lack of washout periods between treatments. In addition, Carley et al. mentioned two side effects of mirtazapine that might impact the health of individuals with OSA, namely weight gain and sedation, and ultimately concluded that mirtazapine should not yet be considered a treatment for OSA.

Oberndorfer et al.(190) (Quality Score: Moderate) examined the effect of theophylline on sleep disorders of different severity, including primary snoring, obstructive snoring, and moderate sleep apnea. Only the results for the moderate sleep apnea category will be reported in this section. It was determined that minimum SaO_2 decreased associated with theophylline therapy when compared to baseline and placebo information (baseline median and percentiles 25/75, 79.6 [72.0/83.3]; placebo 77.5 [64.4/83.2]; and theophylline 76.5 [70.0/81.5]). Oberndorfer et al. ultimately concluded that minimum SaO_2 changes associated with therapeutic theophylline use were not statistically significant.

Rasche et al.(194) (Quality Score: High) examined the efficacy and safety of the bronchodilator salmeterol (trade name: Serevent) as a therapeutic intervention for individuals with OSA. The researchers found, based on the data, that salmeterol was associated with deterioration to SaO_2

measures (baseline 93.2 [SD: 1.9], placebo 93.1 [SD: 2.0], and salmeterol 92.5 [SD: 2.2]). Rasche et al. concluded that this deterioration in SaO_2 was probably of no clinical relevance, and that salmeterol therapy had no influence on OSA.

Surgery and Indirect Measures of Driving Performance

A total of six studies examined for inclusion in the evidence base for Key Question 5 reported on the effect of surgery on at least one indirect measure of driving performance. The primary attributes of these six studies are presented in Table 75.

Table 79. Primary Attributes of Included Studies that Examined the Impact of Surgery

Reference	Year	Study Design	Method of Diagnosis	Prospective or Retrospective	Comparison of Interest	Study Population	Was compliance assessed?
Ferguson et al.(174)	2003	RCT	NR	Prospective	LAUP vs. Control	n = 45 Individuals with mild OSA and complaints of loud snoring	NR
Haraldsson et al.(163)	1995	RCT	PSG	Prospective	UPPP vs. Control	n = 15 Male drivers with habitual symptoms of Rhonchopathy including: OSA – heavy snoring, sleep disturbances and excessive daytime sleepiness with sleep attacks.	NR
Haraldsson et al.(175)	1995	Before After	Questionnaire and a clinical triad of symptoms which confirmed rhonchopathy	Prospective	UPPP vs. Control	n = 172 licensed and regular drivers for previous 5 years and treated for deviated nasal septum or nasal polyposis in 1985 and 1986. n = 123 controls with similar driving experience and no symptoms of rhonchopathy (except possible asymptomatic snoring).	NR
Lojander et al.(183)	1999	RCT	PSG	Prospective	CPAP vs. UPPP	n = 49 Individuals moderately obese, male, aged 18 – 65 years. Previously untreated OSA.	Moderate: 4 hours/night
Lojander et al.(182)	1996	RCT	NR	Prospective	CPAP vs. UPPP vs. conservative treatment	n = 76 Individuals aged 18 – 65 years. Previously untreated OSA.	68% used over 4hours/night
Woodson et al.(199)	2003	RCT	PSG	Prospective	TCRFTA vs. CPAP vs. Placebo	n = 87 Individuals aged 18 – 65 years with self-reported daytime sleepiness. Mild-to-moderate OSA. No prior CPAP or surgical treatment for OSA.	38% used at optimum levels

CPAP = Continuous positive airway pressure; LAUP = Laser assisted uvula palatoplasty; NR = Not reported; OSA = Obstructive sleep apnea; PSG = Polysomnogram; RCT = Randomized controlled trial; TCRFTA = Temperature-controlled radiofrequency tissue ablation; UPPP = Uvulopalatopharyngoplasty.

Quality of Studies that Examined the Effects of Surgery on Indirect Measures of Driving Performance

The purpose of this subsection is to provide details regarding the quality of the included studies that address Key Question 5: Part C. Five of the studies were RCTs, with one of high quality, three of moderate quality, and one of low quality. One additional study utilized a before/after design, and was assessed as having moderate quality. Potential sources for bias in these studies centered around differences between populations such as severity of disease, comorbidities, and the use of self-reported measures. Information about this quality assessment is included in Table 80.

Table 80. Quality of Included Studies that Examined the Impact of Surgery

Reference	Year	Instrument used	Quality
Ferguson et al.(174)	2003	ECRI Institute Quality Assessment Scale I	Moderate
Haraldsson et al.(163)	1995	ECRI Institute Quality Assessment Scale I	High
Haraldsson et al.(175)*	1995	ECRI Institute Quality Item Checklist for Single-Group Studies	Moderate
Lojander et al.(183)	1999	ECRI Institute Quality Assessment Scale I	Moderate
Lojander et al.(182)	2003	ECRI Institute Quality Assessment Scale I	Moderate
Woodson et al.(199)	2003	ECRI Institute Quality Assessment Scale I	Low

Generalizability of Evidence to the Target Population

The purpose of this subsection is to provide details of the extent to which the individuals enrolled in the studies that address Key Question 5: Part C are similar to CMV drivers in the United States. In general, the populations in these studies contain >50% males between the ages of 37 and 64, that may present some similarities to the population predominantly found among CMV drivers in the United States. However, we cannot ascertain from the majority of these studies the extent of driving exposure in the participants, or whether any of them were professional drivers. Thus, our ability to generalize beyond factors such as age or gender is limited. Other important characteristics of the individuals included in the studies that address Key Question 5: Part C are presented in Table 81.

Table 81. Generalizability of Included Studies that Examined the Impact of Surgery

Reference	Year	Type of Sleep Apnea	Mean Age	AHI (Mean, SD)	% Male	Driving Exposure	% CMV Drivers	Generalizability to target population
Ferguson et al.(174)	2003	OSA	44.6 ±8.1 years	10 – 27/hour	NR	NR	NR	NR
Haraldsson et al.(163)	1995	OSA	45 – 64 range	NR	100	NR	NR	NR
Haraldsson et al.(175)	1995	OSA	55 ±8.6	NR	100	1,000 km/year Controls: 18.1 ±13.4 Drivers with SAS (total): 27.2 ±27.9	1,000 km/ year 27.2 ±27.9	NR
Lojander et al.(183)	1999	OSA	51 (41-60)	NR	100	NR	NR	NR
Lojander et al.(182)	2003	OSA	CPAP 51 (38-63) Surgery 47 (27-62)	NR	CPAP 95 Surgery 100	NR	NR	NR
Woodson et al.(199)	2003	OSA	TCRFTA treated 49.4 ±9.2 years CPAP treated 51.7 ±8.6 years Placebo 46.0 ±8.1 years	Placebo:15.4 ±7.8 CPAP:21.3 ±11.1 TCRFTA:19.8 ±9.9	80%	NR	NR	NR

AHI = Apnea-hypopnea index; CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; NR = Not reported; OSA = Obstructive sleep apnea; SAS = Sleep apnea syndrome; SD = Standard deviation; TCRFTA = Temperature-controlled radiofrequency tissue ablation.

Findings of Studies that Assessed Impact of Surgery

Indirect Measures Assessed

The purpose of this subsection is to provide details of the indirect measures assessed in the studies included in the Behavioral Modification Evidence Base. Of the six included studies, two assessed the influence of surgery on AHI, three assessed the influence of surgery on daytime sleepiness, three assessed the influence of surgery on cognitive and psychomotor function, and three assessed the influence of surgery on SaO_2 among individuals with OSA. None of the studies assessed the influence of surgery on blood pressure. The indirect measures are featured in Table 82.

Table 82. Indirect Measures Assessed by Included Studies that Examined the Impact of Surgery

Reference	Year	AHI	Daytime sleepiness	Cognitive and Psychomotor Function	Oxygen Saturation	Blood Pressure
Ferguson et al.(174)	2003	✓				
Haraldsson et al.(163)	1995		✓			
Haraldsson et al.(175)	1995		✓			
Lojander et al.(183)	1999			✓	✓	
Lojander et al.(182)	2003				✓	
Woodson et al.(199)	2003	✓	✓	✓	✓	
Totals		**2**	**3**	**3**	**3**	**0**

AHI = Apnea-hypopnea index.

Impact of Surgery on AHI

Two RCTs examined the impact of two different surgical approaches on AHI among individuals with OSA. Ferguson et al.(174) examined the impact of laser-assisted uvulopalatoplasty (LAUP) and Woodson et al.(199) examined the impact of temperature-controlled radiofrequency tissue ablation (TCRFTA).

Ferguson et al. (Quality Score: Moderate) found that individuals with mild symptomatic OSA who were treated with LAUP experienced a mean reduction in AHI of approximately 21%. 24% of those treated with LAUP were considered treatment successes (defined as an AHI rating of ≤10). 19% of those treated with LAUP achieved a complete response. Among individuals randomized to the control arm of this study (no treatment), 16.7% (4 of 24) were considered treatment successes. No complete responses were observed in the control group. These findings suggest that LAUP has a small positive impact on AHI among individuals with mild symptomatic OSA when compared to the control group. However, individuals who underwent LAUP found that, even postsurgery, there was snoring and OSA symptoms.

Woodson et al.(199) (Quality Score: Low) found no significant impact on AHI among individuals with OSA who were treated with TCRFTA. Individuals assigned to receive TCRFTA experienced an average reduction in AHI of 4.5 (SD: ±13.8) events per hour from a baseline. This reduction from baseline was not statistically significant ($p = 0.34$). Individuals assigned to the sham placebo group also experienced an improvement in AHI from baseline levels, but the reduction was smaller than that experienced by those

who received TCRFTA. AHI at follow-up for individuals in the sham placebo group had a mean of 1.8 events per hour less than was observed at baseline (p = 0.34). A lack of reported information on the CPAP group in this area prevented the reporting of any comparisons for this therapeutic option.

Impact of Surgery on Cognitive and Psychomotor Function

Lojander et al.(183)(Quality Score: Moderate) compared the impact of surgery (UPPP) and CPAP therapy for OSA on cognitive and psychomotor function in an RCT in 50 individuals who were treatment naïve. Cognitive and psychomotor functions were evaluated at baseline, three months post-treatment, and 12 months post-treatment. The authors found that the changes in cognitive and psychomotor function for both groups were insignificant, and posited that the changes seen in these factors may not be accounted for by the instruments most commonly used to test these variables because the changes are not large.

Woodson et al.(199)(Quality Score: Low) examined the effectiveness of multilevel (tongue and palate) TCRFTA compared to CPAP and placebo for the treatment of mild to moderate OSAS. Outcomes for this RCT included AHI, psychomotor vigilance, SaO_2, and daytime sleepiness. The authors found that the TCRFTA group achieved improvement in all of the cognitive and psychomotor functions. The CPAP group also achieved improvement in all of the cognitive and psychomotor functions with the exception of primary outcome, simple reaction time (SRT). When comparing individuals who were compliant with CPAP therapy versus those who were noncompliant, Woodson et al. found no differences between the groups in the three reaction time outcomes tested.

Impact of Surgery on Daytime Sleepiness

Haraldsson et al.(163) (Quality Score: Moderate) compared the long-term effectiveness of UPPP on simulated driving performance. Outcomes assessed included daytime sleepiness and vigilance for 15 male drivers with sleep apnea and 10 controls matched for age and driving experience. Driving performance and daytime sleepiness were reassessed, on average, 45 months following surgery. Self-reported sleepiness score decreased from a preoperative mean value of 137.9 to 86.8 ($p < .01$) in the 13 retested patients. While driving performance of patients improved, no correlation was found between AHI and visual analogue scale. Investigators concluded that the benefits from UPPP on driving performance remains after four years, which may have a substantial impact on traffic safety.

Haraldsson et al.(175) (Quality Score: Moderate) studied crash rate in a sample of UPPP-treated drivers with rhonchopathy. In this case-controlled study, 49 patients who underwent UPPP or laser uvulopalatoplasty (LUPP) and 123 controls that had undergone nasal surgery responded to a two-part questionnaire. The study demonstrated that a return to being a “normal” traffic hazard after UPPP or LUPP was maintained for at least five years.

Woodson et al.(199)(Quality Score: Low) examined the effectiveness of multilevel (tongue and palate) TCRFTA compared to CPAP and placebo for the treatment of mild to moderate OSAS. Outcomes for this RCT included AHI, psychomotor vigilance, SaO_2, and daytime sleepiness. Compared with pretreatment baseline, both TCRFTA and CPAP improved subjective sleepiness measured by ESS ($p<0.05$). Study results demonstrated that TCRFTA and CPAP are both reliable treatments for EDS in mild to moderate OSA patients.

Impact of Surgery on SaO_2

Lojander et al.(182) (Quality Score: Moderate) assessed the effectiveness of CPAP and surgery (UPPP) against conservative management of OSA in this RCT with a population of 76 individuals. The authors found that 100% of the individuals utilizing CPAP therapy had an ODI4 in the normal range; 30% of individuals who had undergone UPPP experienced an ODI4 in the normal range. Lojander et al. concluded that CPAP, with proper compliance, effectively treated OSA, while UPPP had a poor success rate—even among carefully selected patients.

In Woodson et al.(199) (Quality Score: Low) an RCT attempted to determine the efficacy of TCRFTA in the treatment of OSA compared to that of CPAP and sham-placebo in 80 individuals. Altogether, the sham-placebo group SaO_2 levels changed 0.6 (SD: ±4.7) from a baseline of 88.3 (SD: ±3.9) for an effect-size calculated by the authors at 0.15 (P = 0.54). The TCRFTA group SaO_2 levels changed to -3.1 (SD: ±9.5) from a baseline of 86.3 (SD: ±7.6) for an effect-size calculated by the authors at -0.08 (P = 0.81). Final SaO_2 levels were not reported for the CPAP group, negating any comparisons to the sham-placebo or TCRFTA treatments.(199) The authors listed several limitations to the study, including a "limited statistical power, a sham-placebo schedule that was not identical to active treatment, a nonstandard CPAP titration method, incomplete follow-up data, risk of Type 1 error due to multiple testing, and the lack of long-term outcomes assessment."

Summary of Findings

The overall findings of all of our analyses for Key Question 5 are summarized in Table 83.

Table 83. Summary of Findings – Key Question 5

	Behavioral modification (weight loss)	CPAP	Dental Appliances	Medications				Surgery		
			Mandibular Advancement Splints	Theophylline	Modafinil (or armodafinil) as Adjunct to CPAP	Mirtazepine	Salmeterol	UPPP	LAUP	TCRFTA
Crash	No evidence	***	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence	No evidence
Simulated Driving	No evidence	**	*	*	No evidence	No evidence	No evidence	*	No evidence	No evidence
AHI	*	***	*	?	No evidence	*	?	No evidence		
Cognitive/ Psychomotor Function	No evidence	?	?	No evidence	No evidence	No evidence	No evidence	?	?	No evidence
Daytime Sleepiness (ESS)	No evidence	***	?	No evidence	?	No evidence	No evidence	*	?	?
Daytime Sleepiness (MSLT)	No evidence	?	No evidence	No evidence	?	No evidence	No evidence	No evidence	No evidence	No evidence
Daytime Sleepiness (MWT)	No evidence	No evidence	?	No evidence	*	No evidence	No evidence	No evidence	No evidence	No evidence
Oxygen Saturation	?	***	*	?	No evidence	?	?	?	No evidence	?
24-hour Systolic BP	No evidence	**	No evidence	No evidence	No evidence	No evidence	No evidence	?	No evidence	No evidence
24-hour Diastolic BP	No evidence	**	No evidence	No evidence	No evidence	No evidence	No evidence	?	No evidence	No evidence

Technology has a positive impact on this outcome such that crash risk is reduced

Technology has a negative impact on this outcome such that crash risk is increased

Neither a positive nor a negative impact on this outcome has been demonstrated

*** Strength of Evidence = Strong

** Strength of Evidence = Moderate

* Strength of Evidence = Minimally acceptable

? Results equivocal – strength of evidence too weak at present time to draw an evidence–based conclusion (see text for details)

AHI = Apnea-hypopnea index; BP = Blood pressure; CPAP = Continuous positive airway pressure; ESS = Epworth Sleepiness Scale; LAUP = Laser-assisted uvulopalatoplasty; MSLT = Multiple sleep latency test; MWT = Maintenance of wakefulness test; TCRFTA = Temperature-controlled radiofrequency tissue ablation; UPPP = Uvulopalatopharyngoplasty.

Taking all of the findings summarized in the table above into account, we draw the following evidence-based conclusions:

- **CPAP reduces crash risk among individuals with moderate-to-severe OSA (Strength of Evidence: Strong).**
- **While several other technologies may reduce crash risk among individuals with moderate-to-severe OSA, the available evidence to support this is not convincing. Consequently, we refrain from drawing further evidence-based conclusions pertaining to other available technologies at this time.**

Key Question 6: What is the length of time required following initiation of an effective treatment (determined by Key Question 5) for patients with OSA to reach a degree of improvement that would permit safe driving (as determined by crash rates or through indirect measures of crash risk)?

Our assessment of the evidence pertaining to Key Question 5 demonstrated that the average driver with OSA is at a significantly increased risk for a motor vehicle crash when compared with comparable drivers who do not have the disorder. Currently it is understood that there is little evidence to help advise individuals with OSA when driving can be safely restarted after beginning treatment, or whether it is safe to continue driving if treatment is missed for a few nights.(159)

In this section of the evidence report we attempt to identify the length of time required following initiation of an effective treatment for individuals with OSA to reach a degree of improvement that would permit safe driving (as determined through indirect measures of crash risk, i.e., driving simulators or cognitive/psychomotor functioning) or to show improvement in the risk factors associated with OSA (i.e., disease severity, daytime sleepiness, SaO_2, blood pressure).

Identification of Evidence Base

To meet the aims of this section of the evidence report we searched for trials that were designed to assess the time course of changes in indirect measures of crash risk or risk factors associated with OSA among individuals with OSA. Studies were limited to those whose follow-up times were two weeks or less for treatment with CPAP, medication, and oral appliances, and one month or less for treatment with surgery. Any changes in performance occurring at follow-up times longer than two weeks or one month were addressed in Key Question 5.

The identification pathway for the evidence base for Key Question 6 is summarized in Figure 47. Our searches[18] identified a total of 781 articles that appeared relevant to both Key Question 5 and 6. Following application of the retrieval criteria for this particular key question, 232 full-length articles were retrieved and read in full. Twenty-four of these 232 retrieved articles were found to meet the inclusion criteria[19] for Key Question 6 (Table 90.). Table D-1 of Appendix D lists the 208 articles that were retrieved but then excluded and provides the reason for their exclusion.

[18] See Appendix A for search strategies
[19] See Appendix C for inclusion criteria

Figure 47. Development of Evidence Base for Key Question 6

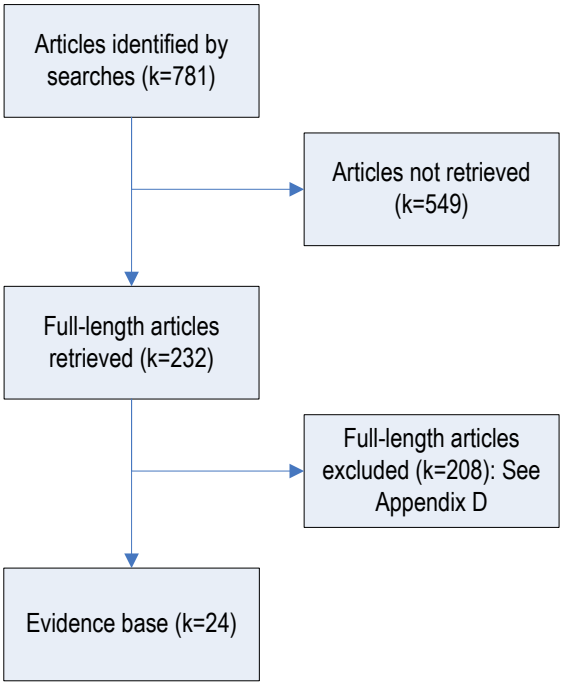


Table 84. Evidence Base for Key Question 6

Reference	Year	Study Location	Country
Continuous Positive Airway Pressure (CPAP)			
Loredo et al.(184)	2006	California	USA
Norman et al.(189)	2006	California	USA
Orth et al.(158)	2005	Bochum	Germany
Turkington et al.(159)	2004	Leeds	United Kingdom
Bao et al.(202)	2002	California	USA
Wiest et al.(203)	2002	Erlangen	Germany
Bardwell et al.(165)	2001	California	USA
Randerath et al.(204)	2001	Hagen	Germany
Ficker et al.(205)	2000	Erlangen	Germany
Teschler et al.(206)	2000	Essen	Germany
Sharma et al.(207)	1996	Manitoba	Canada
Valencia-Flores et al.(208)	1996	California	USA
Continuous Positive Airway Pressure (CPAP) and Oral Appliances			
Randerath et al.(209)	2002	Hagen	Germany
Continuous Positive Airway Pressure (CPAP) and Medication			
Saletu et al.(210)	1999	Vienna	Austria
Medication			
Carley et al.(169)	2007	Illinois	USA
Kingshott et al.(100)	2001	Edinburgh	United Kingdom
Pack et al.(101)	2001	Multicenter (22 centers in the United States: Pennsylvania, California, Oklahoma, and Massachusetts)	USA
Hein et al.(176)	2000	Grobhansdorf	Germany
Oberndorfer et al.(190)	2000	Vienna	Austria
Rasche et al.(194)	1999	Bochum	Germany
Ferber et al.(211)	1993	Lyon	France
Cook et al.(212)	1989	South Carolina	USA
Espinoza et al.(213)	1987	Adelaide	South Australia
Oral Appliances			
Mehta et al.(214)	2001	New South Wales	Australia

Evidence Base

The key characteristics of the 24 included studies that address Key Question 6 are presented in Table 85. Detailed information pertinent to this section that has been extracted from included studies is presented in the Study Summary Tables that can be found in Appendix G.

Table 85. Key Study Design Characteristics of Studies that Address Key Question 6

Reference	Year	Study Design	Primary Purpose of Study	Time Points Assessed	Outcomes Assessed
Continuous Positive Airway Pressure (CPAP)					
Loredo et al.(184)	2006	Randomized, double-blind, placebo-controlled, parallel trial	To investigate the short-term effectiveness of CPAP and oxygen in improving sleep quality in individuals with OSA	1 and 14 days	ESS, AHI, SpO_2
Norman et al.(189)	2006	Randomized, double-blind, placebo-controlled trial	To examine the differential effects of 2 weeks of CPAP versus 2 weeks of sham-CPAP on 24-hour ambulatory blood pressure in a group of individuals with OSA who were not on antihypertensive medications	14 days	AHI, ODI (≥3%), SpO_2, SpO_2 nadir during desaturations, blood pressure
Orth et al.(158)	2005	Prospective case series	To assess accident rates using a driving simulator in individuals with OSAS before and during CPAP therapy	2 days	ESS, Reaction time, accident frequency, frequency of concentration faults
Turkington et al.(159)	2004	Controlled trial	To assess the time course of changes in driving simulator performance in individuals with SAHS following treatment with CPAP	1, 3, and 7 days	Tracking error, reaction time, off-road events per hour, SSS
Bao et al.(202)	2002	Randomized, double-blind, placebo-controlled trial	To assess the relationship between SNS activity and 24-hour blood pressure variability in individuals with OSA, and the effect of CPAP on blood pressure variability	7 days	Systolic and diastolic blood pressure variability, mean arterial pressure variability
Wiest et al.(203)	2002	Randomized, cross-over trial	To investigate whether prophylactic heated humidifier during the initiation of CPAP would result in improved initial comfort and acceptance in individuals with OSA	2 nights	ESS score
Bardwell et al.(165)	2001	Randomized, placebo-controlled trial	To determine whether 1-week CPAP treatment, compared with placebo CPAP, improves cognitive functioning in individuals with OSA	7 days	RDI, apneas, hypopneas, SaO_2 levels, Wechsler Adult Intelligence Scale-Revised Digit Symbol and Digit Span, Trailmaking A/B, Digit Vigilance, Stroop Color-Word, Digit Ordering, and Word Fluency tests
Randerath et al.(204)	2001	Randomized, single-blind, cross-over trial	To establish whether impedance-controlled self-adjusting positive airway pressure therapy is equally as good as constant continuous positive airway pressure in the treatment of OSAS	2 nights	AHI, minimal SaO_2
Ficker et al.(205)	2000	Randomized, cross-over trial	To evaluate the therapeutic efficacy of a novel auto-CPAP device based exclusively on the forced oscillation technique compared to conventional CPAP in individuals with OSA	2 nights	AI, AHI, ODI (≥4%), ESS
Teschler et al.(206)	2000	Randomized, double-blind, cross-over trial	To test whether auto adjusting nasal CPAP greatly reduces AHI compared with manually titrated conventional nasal CPAP in individuals with OSAS	1 night	AI, AHI
Sharma et al.(207)	1996	Randomized, cross-over trial	To evaluate the treatment of OSA with self-titrating CPAP compared to conventional, manually adjusted CPAP	2 nights	AHI, obstructive apneas, obstructive hypopneas, number of SaO_2 dips, lowest SaO_2

Reference	Year	Study Design	Primary Purpose of Study	Time Points Assessed	Outcomes Assessed
Valencia-Flores et al.(208)	1996	Prospective case-series	To evaluate cognitive function in individuals with sleep apnea after acute nasal CPAP treatment	After 2 nights	RDI, SaO_2, Benton Visual Retention Test, Finger Oscillation, Wilkinson Addition Test, Digit Symbol from the Wechsler Adult Intelligence Scale, Auditory Verbal Learning Test
Continuous Positive Airway Pressure (CPAP) and Oral Appliances					
Randerath et al.(209)	2002	Randomized, cross-over trial	To compare an individually adjustable ISAD that permits movements of the lower jaw in three dimensions, with CPAP in the treatment of individuals with an AHI ≤30/hour	1 night	AHI, SaO_2
Continuous Positive Airway Pressure (CPAP) and Medication					
Saletu et al.(210)	1999	Randomized, cross-over trial	To compare the efficiency of pneumological therapy by nasal CPAP versus a pharmacologic approach with theophylline on respiratory variables as well as objective and subjective sleep and awakening quality in individuals with moderate sleep apnea measured by PSG and psychometry	1 night	AHI, AI, ODI (≥4%), minimum SaO_2, sleep latency, drowsiness, the Grünberger alphabetical cancellation test for quantification of attention, concentration and attention variability, the numerical memory test, the Grünberger fine motor activity test for evaluation of changes in psychomotor activity and drive, reaction time, reaction time variability, errors of omission and commission, diastolic and systolic blood pressure
Medication					
Carley et al.(169)	2007	Randomized, double-blind, placebo-controlled, 3-way cross-over trial	To determine whether mirtazapine, a mixed 5-HT_2/5-HT_3 antagonist that also promotes serotonin release in the brain, would effectively reduce AHI during both NREM and REM sleep in individuals with OSA	7 days	AI, HI, AHI, minimum SaO_2, ODI (>3%), SSS
Kingshott et al.(100)	2001	Randomized, double-blind, placebo-controlled cross-over trial	To determine the efficacy and safety of the novel wake-promoting medication modafinil in the treatment of CPAP-resistant daytime sleepiness in individuals with SAHS	14 days	ESS, MSLT, MWT, SteerClear, a SURT task, Trail Making, PASAT
Pack et al.(101)	2001	Randomized, double-blind, placebo-controlled, parallel group trial	To assess the efficacy and safety of modafinil for the treatment of residual daytime sleepiness in individuals with OSAHS	7 days	ESS
Hein et al.(176)	2000	Randomized, double-blind, placebo-controlled cross-over trial	To evaluate the parameters defining OSAHS over a seven-day period of theophylline treatment in order to compare its potential effect on night-to-night variability	7 days	AHI
Oberndorfer et al.(190)	2000	Single-blind, placebo-controlled cross-over trial	To determine the efficiency of theophylline concerning respiratory variables as well as objective and subjective sleep and awakening quality in individuals with primary snoring, obstructive snoring, and moderate sleep apnea	1 night	AHI, AI, ODI (≥4%), minimum SaO_2, sleep latency, drowsiness, the Grünberger alphabetical cancellation test for quantification of attention, concentration and attention variability, the numerical memory test, the Grünberger fine motor activity test for evaluation of changes in psychomotor activity and drive, reaction time, reaction time variability, errors of omission and commission

Reference	Year	Study Design	Primary Purpose of Study	Time Points Assessed	Outcomes Assessed
Rasche et al.(194)	1999	Randomized, double-blind, placebo-controlled cross-over trial	To obtain data on the efficacy and safety of salmeterol in individuals with OSAS	1 night	AI, HI, AHI, SaO_2, minimum SaO_2
Ferber et al.(211)	1993	Randomized, double-blind, placebo-controlled cross-over trial	To investigate the relationships between the effects on blood-gas and on sleep patterns of the oral opiate antagonist naltrexone in OSAS	1 night	AHI
Cook et al.(212)	1989	Randomized, double-blind, placebo-controlled cross-over trial	To determine whether MPA therapy at higher dosage levels has any significant effect on the indices of severity of OSA syndrome	7 days	Number of disordered breathing events per hour of sleep, arterial SaO_2 during disordered breathing
Espinoza et al.(213)	1987	Randomized, single-blind, placebo-controlled cross-over trial	To investigate the effects of aminophylline on both sleep architecture and the disordered pattern of breathing in individuals with OSAS	1 night	AI, HI, sleep latency, SaO_2, minimum SaO_2
Oral Appliances					
Mehta et al.(214)	2001	Randomized, controlled, three-period cross-over trial	To systematically investigate the efficacy of a novel MAS in individuals with OSA	7 days	ESS, AHI, minimum SaO_2

AHI = Apnea-hypopnea index; AI = Apnea index (number of apneas per hour); CPAP = Continuous positive airway pressure; ESS = Epworth Sleepiness Scale; HI = Hypopnea index (number of hypopneas per hour); ISAD = Intraoral sleep apnea device; MAS = Mandibular advancement splint; MPA = Medroxyprogresterone acetate; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; NREM = Non-rapid eye movement; ODI = Oxygen desaturation index; OSA = Obstructive sleep apnea; OSAHS = Obstructive sleep apnea/hypopnea syndrome; OSAS = Obstructive sleep apnea syndrome; PASAT = Paced auditory serial addition task; PSG = Polysomnogram; RDI = Respiratory disturbance index; SAHS = Sleep apnea hypopnea syndrome; SaO_2 = Oxygen saturation (%); SNS = Sympathetic nervous system; SpO_2 = Oxyhemoglobin saturation; SSS = Stanford Sleepiness Scale; SURT = Simple unprepared response time.

Quality of Evidence Base

The results of our assessment of the overall quality of the evidence base for Key Question 6 are presented in Table 86. Complete details of our quality assessment can be found in the Study Summary Tables presented in Appendix G.

Table 86. Quality of Studies for Key Question 6

Reference	Year	Quality Scale Used	Quality
Continuous Positive Airway Pressure (CPAP)			
Loredo et al.(184)	2006	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Norman et al.(189)	2006	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Orth et al.(158)	2005	ECRI Institute Quality Scale III: Pre-Post Trials	Low
Turkington et al.(159)	2004	ECRI Institute Quality Scale I: Controlled Trials	High
Bao et al.(202)	2002	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Wiest et al.(203)	2002	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Bardwell et al.(165)	2001	ECRI Institute Quality Scale I: Controlled Trials	High
Randerath et al.(204)	2001	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Ficker et al.(205)	2000	ECRI Institute Quality Scale I: Controlled Trials	High
Teschler et al.(206)	2000	ECRI Institute Quality Scale I: Controlled Trials	High
Sharma et al.(207)	1996	ECRI Institute Quality Scale I: Controlled Trials	High
Valencia-Flores et al.(208)	1996	ECRI Institute Quality Scale III: Pre-Post Trials	Low
Continuous Positive Airway Pressure (CPAP) and Oral Appliances			
Randerath et al.(209)	2002	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Continuous Positive Airway Pressure (CPAP) and Medication			
Saletu et al.(210)	1999	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Medication			
Carley et al.(169)	2007	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Kingshott et al.(100)	2001	ECRI Institute Quality Scale I: Controlled Trials	High
Pack et al.(101)	2001	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Hein et al.(176)	2000	ECRI Institute Quality Scale I: Controlled Trials	High
Oberndorfer et al.(190)	2000	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Rasche et al.(194)	1999	ECRI Institute Quality Scale I: Controlled Trials	High
Ferber et al.(211)	1993	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Cook et al.(212)	1989	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Espinoza et al.(213)	1987	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Oral Appliances			
Mehta et al.(214)	2001	ECRI Institute Quality Scale I: Controlled Trials	Moderate

Generalizability of Evidence to Target Population

Important characteristics of the individuals represented in the 24 studies that comprise the evidence base for Key Question 6 are presented in Table 87. The age range of the private motor vehicle license holders included in these studies (28 to 72) is similar to those of CMV drivers. Women tend to be overrepresented in studies involving private motor vehicle drivers. However, the number of males included in these studies ranged from 58% to 100%, which may present some similarities to the population predominantly found among CMV drivers in the United States. We cannot ascertain from the data reported in these studies the extent of driving exposure in the participants, or whether any of them were professional drivers. Thus, our ability to generalize beyond factors such as age or gender is limited. It is unclear whether the ethnicity of the private motor vehicle license holders included in these studies is representative of CMV drivers due to lack of reporting.

Whether the differences between the individuals enrolled in the included studies and the average CMV driver are important for this particular outcome is debatable. It seems unlikely that the time taken for a treatment to become effective among CMV drivers will differ markedly from other populations.

Table 87. Individuals with OSA Enrolled in Studies that Address Key Question 6

Reference	Year	Number of Individuals Included In Study (n =)	Age Distribution	% Male	% CMV Drivers	Ethnicity (%)	Generalizability to Target Population
Continuous Positive Airway Pressure (CPAP)							
Loredo et al.(184)	2006	**CPAP:** 22 **Placebo:** 19 **Oxygen:** 22	**CPAP:** 48.2 ±10.9 **Placebo:** 48.3 ±11.2 **Oxygen:** 43.4 ±8.6	**CPAP:** 82 **Placebo:** 84 **Oxygen:** 73	NR	NR	Unclear
Norman et al.(189)	2006	**CPAP:** 18 **Placebo:** 15 **Oxygen:** 13	**CPAP:** 49.7 ±2.5† **Placebo:** 49.3 ±2.7† **Oxygen:** 44.2 ±2.4†	**CPAP:** 83 **Placebo:** 87 **Oxygen:** 69	NR	**CPAP / Placebo / Oxygen** **Caucasian:** 61 / 67 / 62 **African American:** 11 / 7 / 23 **Hispanic:** 11 / 13 / 8 **Asian:** 11 / 0 / 8 **Other:** 6 / 13 / 0	Unclear
Orth et al.(158)	2005	31	55.3 ±10.2	100	NR	NR	Unclear
Turkington et al.(159)	2004	**CPAP:** 18 **Control:** 18	**CPAP:** 49.9 ±10 **Control:** 51.7 ±12.2	**CPAP:** 94 **Control:** 94	NR	NR	Unclear
Bao et al.(202)	2002	**CPAP:** 23 **Placebo:** 18	**CPAP:** 46.2 ±1.8† **Placebo:** 49.7 ±2.2†	**CPAP:** 74 **Placebo:** 89	NR	NR	Unclear
Wiest et al.(203)	2002	44	54.1 ±9.7	80	NR	NR	Unclear
Bardwell et al.(165)	2001	**CPAP:** 20 **Placebo:** 16	**CPAP:** 47 ±1.9† **Placebo:** 48 ±2.2†	81	NR	NR	Unclear
Randerath et al.(204)	2001	25	52.8 ±9.0	80	NR	NR	Unclear
Ficker et al.(205)	2000	18	50.6 ±10.5	100	NR	NR	Unclear
Teschler et al.(206)	2000	10	52 ±2†	100	NR	NR	Unclear
Sharma et al.(207)	1996	20	48.1 ±10.4	95	NR	NR	Unclear
Valencia-Flores et al.(208)	1996	37	48.5 ±8.9	78	NR	**Caucasian:** 75.7 **African American:** 10.8 **Hispanic:** 2.7 **Asian:** 10.8	Unclear
Continuous Positive Airway Pressure (CPAP) and Oral Appliances							
Randerath et al.(209)	2002	20	56.5 ±10.2	80	NR	NR	Unclear
Continuous Positive Airway Pressure (CPAP) and Medication							
Saletu et al.(210)	1999	13	58.1 ±8.7	100	NR	NR	Unclear

Reference	Year	Number of Individuals Included In Study (n =)	Age Distribution	% Male	% CMV Drivers	Ethnicity (%)	Generalizability to Target Population
Medication							
Carley et al.(169)	2007	12	Males: 39 ±18.3 Females: 43.4 ±14.2	58	NR	NR	Unclear
Kingshott et al.(100)	2001	30	53 ±7	90	NR	NR	Unclear
Pack et al.(101)	2001	**Modafinil:** 77 **Placebo:** 80	**Modafinil:** 50 (32-76)‡ **Placebo:** 50 (28-72)‡	**Modafinil:** 79 **Placebo:** 74	NR	NR	Unclear
Hein et al.(176)	2000	14	50 ±8	86	NR	NR	Unclear
Oberndorfer et al.(190)	2000	11	55.5 ±9.3	91	NR	NR	Unclear
Rasche et al.(194)	1999	20	53 ±7.8	80	NR	NR	Unclear
Ferber et al.(211)	1993	12	60.3 (42-79)‡	83	NR	NR	Unclear
Cook et al.(212)	1989	10	51 ±3.2†	100	NR	NR	Unclear
Espinoza et al.(213)	1987	10	52.6 ±3.6†	100	NR	NR	Unclear
Oral Appliances							
Mehta et al.(214)	2001	24	48 ±9	79	NR	NR	Unclear

Data are expressed as mean ±SD; †Data expressed as mean ±SEM; ‡Data expressed as mean (range); CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; NR = Not reported.

Table 88. Outcomes Assessed for Key Question 6

Study	Year	Driving Simulator	Sleepiness	Severity of Disordered Respiration	Oxygen Saturation	Blood Pressure	Psychomotor/ Cognitive Functioning
Continuous Positive Airway Pressure (CPAP)							
Loredo et al.(184)	2006		✓	✓	✓		
Norman et al.(189)	2006			✓	✓	✓	
Orth et al.(158)	2005	✓	✓				✓
Turkington et al.(159)	2004	✓	✓				
Bao et al.(202)	2002					✓	
Wiest et al.(203)	2002		✓				
Bardwell et al.(165)	2001			✓			✓
Randerath et al.(204)	2001			✓	✓		
Ficker et al.(205)	2000		✓	✓			
Teschler et al.(206)	2000			✓			
Sharma et al.(207)	1996			✓	✓		
Valencia-Flores et al.(208)	1996			✓	✓		✓
Continuous Positive Airway Pressure (CPAP) and Oral Appliances							
Randerath et al.(209)	2002			✓	✓		
Continuous Positive Airway Pressure (CPAP) and Medication							
Saletu et al.(210)	1999		✓	✓	✓	✓	✓
Medication							
Carley et al.(169)	2007		✓	✓	✓		
Kingshott et al.(100)	2001		✓				✓
Pack et al.(101)	2001		✓				
Hein et al.(176)	2000			✓			
Oberndorfer et al.(190)	2000		✓	✓	✓		✓
Rasche et al.(194)	1999			✓	✓		
Ferber et al.(211)	1993			✓			
Cook et al.(212)	1989			✓	✓		
Espinoza et al.(213)	1987		✓	✓	✓		
Oral Appliances							
Mehta et al.(214)	2001		✓	✓	✓		
Number of Studies		**2**	**12**	**18**	**13**	**3**	**6**

Findings

The individual findings of each of the 24 studies that address Key Question 6 are presented in detail in Appendix G. Some or all of these studies presented data on indirect measures of crash risk, as seen in Table 88 (i.e., driving simulator performance, presence and degree of daytime sleepiness, severity of disordered breathing during sleep, nighttime SaO_2, blood pressure, psychomotor/cognitive functioning). Within each subsection we then present the findings of any study that reported data on the outcome of interest for any OSA treatment, provided the follow-up period was two weeks or less for CPAP, medication, and oral devices, or one month or less for surgical treatments.

Driving Simulator Performance

Two included studies reported data on driving simulator performance following treatment in individuals with OSA (see Table 88).(158,159) Both studies assessed performance following CPAP treatment. No studies that evaluated the effects of medication, oral appliances, or surgical treatments on driving simulator performance *and* met our inclusion criteria were identified.

Both studies had findings that indicated significant improvements in driving performance following two days of CPAP use. Orth et al.(158) (Quality Score: Low) reported significant reduction of crashes and concentration faults after two days of CPAP therapy, with the improvements continuing throughout the therapeutic course. Turkington et al.(159) (Quality Score: High) reported that driving simulator performance was significantly better in the CPAP-treated group than in the controls after seven days of CPAP therapy.

Presence and Degree of Daytime Sleepiness

Twelve included studies reported data on daytime sleepiness following treatment in individuals with OSA (see Table 88).(100,101,158,159,169,184,190,203,205,210,213,214)

Six of the 12 included studies (Quality Rating: High) provided data assessing the relationship between daytime sleepiness and treatment with CPAP. Six of the 12 included studies (Quality Rating: Moderate) provided data assessing the relationship between daytime sleepiness and treatment with medications. One of the 12 included studies (Quality Rating: Moderate) provided data assessing the relationship between daytime sleepiness and treatment with oral appliances. No studies that both evaluated the effects of surgical treatments on daytime sleepiness *and* met our inclusion criteria were identified.

The findings from the 12 studies included in this section of the evidence report are presented below.

CPAP

The results of these six studies indicate that with CPAP treatment, individuals with OSA show significant improvement in daytime sleepiness after as little as one night of treatment. In Loredo et al.(184), all groups tested demonstrated improvements in daytime sleepiness with treatment; however, the CPAP group demonstrated the greatest reduction in daytime sleepiness. Orth et al.(158), Turkington et al.(159), Wiest et al.(203), and Ficker et al.(205) reported that average ESS scores improved significantly during CPAP therapy, with the mean ESS scores for each study falling below 9 (highest SD 4.8). Saletu et al.(210) reported that sleep latency improved among individuals who underwent CPAP therapy.

Medication

In Carley et al.(169), mirtazapine was associated with an improvement in the ability to “function at high level, but not at peak; able to concentrate” on the Stanford Sleepiness Scale. Pack et al.(101) found that adjunct modafinil therapy appeared to reduce subjectively measured daytime sleepiness after seven days of treatment. Kingshott et al.(100) also investigated the effect of modafinil on daytime sleepiness and found an improvement in the MWT, indicating a positive association between the pharmacotherapy sleepiness. The remaining three studies (Saletu et al.(210), Oberndorfer et al.(190), and Espinoza et al.(213)) found that modafinil, theophylline, and aminophylline did not significantly affect the measures of daytime sleepiness examined.

Oral Appliances

The results of the single included study (Mehta et al.(214)) reported a significant improvement in daytime sleepiness as measured by the ESS, suggesting that MASs may provide significant improvement in daytime sleepiness after one week of treatment.

Severity of Disordered Respiration During Sleep

Eighteen included studies reported data on severity of disordered respiration during sleep following treatment in individuals with OSA (see Table 88).(165,169,176,184,189,190,194,204-214)

Ten of the 18 included studies provided data regarding severity of disordered respiration during sleep and treatment with CPAP. Eight of the 18 included studies provided data regarding severity of disordered respiration during sleep and treatment with medications. Two of the 18 included studies provided data regarding severity of disordered respiration during sleep and treatment with oral appliances. No studies that both evaluated the effects of surgical treatments on severity of disordered respiration during sleep *and* met our inclusion criteria were identified.

The findings from the 18 studies included in this section of the evidence report are presented below.

CPAP

The results of these 10 studies indicate that with CPAP treatment, individuals with OSA show significant improvement in severity of disordered respiration during sleep after as little as one night of treatment. Studies that demonstrated improvement with a single night of treatment included Loredo et al.(184), Randerath et al.(204), Ficker et al.(205),Teschler et al.(206), Sharma et al.(207), and Saletu et al.(210) An improvement with two nights of CPAP treatment was demonstrated in Valencia-Flores et al.(208) Improvement in the severity of disordered respiration during sleep was investigated over somewhat longer periods of time in Loredo et al.(184) (1 night to 2 weeks), Norman et al.(189) (2 weeks), and Bardwell et al.(165) (1 week). Each of the studies reported that CPAP therapy was effective in treating disordered respiration during sleep.

Medication

The efficacy of medication therapy on the severity of disordered breathing during sleep was mixed. Two studies demonstrated a positive effect on the severity of SDB in with medication: Hein et al.(176) reported a small but significant decrease in AHI following treatment with theophylline; while Ferber et al.(211) reported that two nights of naltrexone administration for the treatment of severity of disordered respiration during sleep was followed by a significant reduction of AHI. The remaining six studies demonstrated no significant difference in the severity of disordered breathing during sleep with pharmacotherapy, including: Saletu et al.(210) (theophylline); Carley et al.(169) (mirtazapine); Oberndorfer et al.(190) (theophylline); Rasche et al.(194) (salmeterol); Cook et al.(212) (medroxyprogesterone acetate); and Espinoza et al.(213) (aminophylline).

Oral Appliances

The results of the two studies in this evidence base demonstrated that oral appliances are effective in reducing the severity of disordered respiration during sleep (as measured by the AHI) in individuals with OSA after one night of treatment (Randerath et al.(209)) and one week of treatment (Mehta et al.(214)).

SaO_2

Thirteen included studies reported data on SaO_2 during sleep following treatment in individuals with OSA (see Table 88).(169,184,189,190,194,204,207-210,212-214)

Seven of the 13 included studies (Quality Rating: Moderate) provided data regarding SaO_2 during sleep and treatment with CPAP. Six of the 13 included studies (Quality Rating: Moderate) provided data regarding severity of disordered respiration during sleep and treatment with medications. Two of the 13 included studies (Quality Rating: Moderate) provided data regarding severity of disordered respiration during sleep and treatment with oral appliances. No studies evaluating the effects of surgical treatments on severity of disordered respiration during sleep were identified that met our inclusion criteria.

The findings from the 13 studies included in this section of the evidence report are presented below.

CPAP

The results of all seven studies included in this evidence base indicate significant improvement in several measures of SaO_2 (minimum SaO_2, number of oxygen dips, and mean SaO_2) during sleep with CPAP treatment in individuals with OSA. Some of these differences were noted after only a single night of treatment (Loredo et al.(184), Randerath et al.(204), Sharma et al.(207), and Randerath et al.(209)); while in other studies, the improvement in SaO_2 was demonstrated at 2 nights treatment (Valencia-Flores et al.(208) and at 2 weeks of CPAP therapy (Norman et al.(189)).

Medication

In studies that observed the effect of medication on SaO_2 levels in individuals with OSA, it was found that the administration of theophylline (Saletu et al.(210), Oberndorfer et al.(190), and Espinoza et al.(213)) salmeterol (Rasche et al.(194), aminophylline (Espinoza et al.(213), or mirtazapine (Carley et al.(169) for one day had no significant effect on any measure of SaO_2. Similarly, the administration of medroxyprogesterone acetate (MPA) (Cook et al.(212) for seven days had no significant effect on any measure of SaO_2.

Oral Appliances

The results of the two included studies are mixed. Randerath et al.(214) reported that oral appliances were effective in significantly increasing minimum SaO_2 during sleep in individuals with OSA after one week of treatment, whereas Mehta et al.(209) reported that oral appliances did not significantly change minimum SaO_2 after one night of treatment .

Blood Pressure

Three included studies reported data on blood pressure following treatment in individuals with OSA (see Table 88).(189,202,210)

All three included studies provided data regarding blood pressure and treatment with CPAP. One of the three included studies provided data regarding blood pressure and treatment with medications. No studies evaluating the effects of oral appliances and surgical treatments on blood pressure were identified that met our inclusion criteria.

The findings from the three studies included in this section of the evidence report are presented below.

CPAP

In summary, the results of these three studies were mixed. Taken as a group, however, they indicated that CPAP therapy was associated with an improvement in blood pressure in individuals with OSA. Specifically, the included studies demonstrated that there were significant improvements in blood pressure following two weeks of treatment, but not after one night or one week of treatment. In Norman et al.(189), the authors reported that two weeks of CPAP therapy resulted in declines in nighttime systolic, mean, and diastolic blood pressure as well as declines in daytime mean and diastolic blood pressure. Bao et al.(202) found there was no effect specific to the CPAP group, since the blood pressure variability of both CPAP and placebo-CPAP groups declined equivalently over the one-week trial. In a similar study by Saletu et al.(210), the authors reported no significant differences between baseline and one night of CPAP treatment in systolic pressure in the morning and evening, as well as diastolic pressure in the morning and evening.

Medication

In an investigation of the effects of theophylline on blood pressure, Saletu et al.(210) reported that there were no significant differences between baseline and one night of theophylline treatment in systolic pressure in the morning and evening, as well as diastolic pressure in the morning and evening.

Psychomotor/Cognitive Functioning

Six included studies reported data on psychomotor and cognitive functioning following treatment in individuals with OSA (see Table 88).(100,158,165,190,208,210)

Four of the six included studies provided data regarding psychomotor and cognitive functioning following treatment with CPAP. Three of the six included studies provided data regarding psychomotor and cognitive functioning following treatment with medications. No studies evaluating the effects of oral appliances or surgical treatments on psychomotor and cognitive functioning were identified that met our inclusion criteria.

The findings from the six studies included in this section of the evidence report are presented below.

CPAP

The results of the four included studies indicated that with CPAP, treatment individuals with OSA demonstrated significant improvement in some measures of psychomotor and cognitive functioning, such as alertness, attention, and overall cognitive functioning, after as little as one night of treatment. Improvements were seen in alertness and divided attention, but not vigilance, in Orth et al.(158) A similar study by Bardwell et al.(165) found that only one (Digit Vigilance-Time) of the 22 scores of cognitive and psychomotor function showed significant changes specific to one week of CPAP treatment: the CPAP group also demonstrated better overall cognitive functioning post-treatment than the placebo group. Valencia-Flores et al.'s(208) study of the effect of CPAP on cognitive and psychomotor functioning found that individuals attempted more problems and were more accurate following two nights of treatment on nasal CPAP as measured by the Wilkinson Addition Test. However, they showed no significant differences in the Finger Oscillation, Digit Symbol of the Wechsler Adult Intelligence Scale (WAIS), Rey Auditory Verbal Learning Test, and the Benton Visual Retention Test. Saletu et al.(210) found that reaction time errors of commission and omission were both significantly reduced following one night of treatment on CPAP. However, they also found that there were no

significant differences in attention, attention variability, numerical memory, fine motor activity, reaction time, and reaction time variability.

Medication

The three included studies reporting on the effect of pharmacotherapy on cognitive and psychomotor functioning demonstrated some significant differences in effectiveness along with inconsistencies in results. Overall, however, the effect of medication on cognitive and psychomotor function in individuals with OSA could be considered mixed. Saletu et al.(210) found that theophylline therapy was associated with a reduction in reaction time errors of commission and omission, but not with attention, attention variability, numerical memory, fine motor activity, reaction time, and reaction time variability. Two weeks of modafinil had no significant effect on any measure of psychomotor and cognitive functioning. In another study of theophylline and cognitive and psychomotor function in individuals with OSA, Oberndorfer et al.(190) found improved reaction times, but no difference in errors of omission and commission; differences in attention, concentration, numerical memory; and fine motor performance in the theophylline and the placebo nights. Kingshott et al.'s(100) study of the effect of modafinil on cognitive and psychomotor function among individuals with OSA found that there were no significant treatment-related improvements in cognitive performance as measured by the digit symbol test.

Summary of Findings

Driving Simulator Performance

Individuals with OSA show significant improvement in driving simulator performance after two days of CPAP treatment. (Strength of Evidence: Weak)

Two high-quality studies assessed driving simulator performance in individuals with OSA following CPAP treatment. One of these studies(159) was specifically designed to assess the time course of changes in driving simulator performance in individuals with severe sleep apnea/hypopnea syndrome and hypersomnolence during two weeks of CPAP treatment. Both of these studies demonstrated that performance on a driving simulator improves following CPAP treatment.

Due to a paucity of data, no conclusion pertaining to the length of time required for medication, oral appliances, or surgery to improve driving simulator performance in individuals with OSA is drawn.

No studies met the inclusion criteria for this key question.

Presence and Degree of Daytime Sleepiness

Individuals with OSA show significant improvement in daytime sleepiness after one night of CPAP treatment. (Strength of Evidence: Weak)

Due to a paucity of data, no conclusion pertaining to the length of time required for medication, oral appliances, or surgery to improve daytime sleepiness in individuals with OSA is drawn at this time.

Severity of Disordered Respiration During Sleep

Individuals with OSA show significant improvement in severity of disordered respiration during sleep after one night of CPAP treatment. (Strength of Evidence: Weak)

Individuals with OSA show significant improvement in severity of disordered respiration during sleep after one night of treatment with theophylline. (Strength of Evidence: Weak)

Three moderate-to-high quality studies assessed severity of disordered respiration during sleep in individuals with OSA following treatment with theophylline. These three studies consistently demonstrated that severity of disordered respiration during sleep (as measured using AHI) improves following theophylline treatment.

Due to a paucity of data, no conclusion pertaining to the length of time required for mirtazapine, salmeterol, aminophylline, or MPA therapy to improve severity of disordered respiration during sleep in individuals with OSA is drawn.

Five moderate-to-high quality studies (one study for each treatment) assessed severity of disordered respiration during sleep in individuals with OSA following treatment with a medication. These studies found that mirtazapine significantly reduces AHI after seven days of treatment, and that naltrexone reduces AHI after two days of treatment. On the other hand, one night of salmeterol or aminophylline, as well as seven days of MPA therapy, did not significantly change the severity of disordered breathing during sleep.

Due to a paucity of data, no conclusion pertaining to the length of time required for oral appliances to improve severity of disordered respiration during sleep in individuals with OSA is drawn.

Two moderate-quality studies assessed severity of disordered respiration during sleep in individuals with OSA following treatment with two different oral appliances. These two studies reported that their respective oral appliances were effective in significantly reducing the severity of disordered respiration during sleep (as measured by the AHI) in individuals with OSA after one night and one week of treatment.

Due to a paucity of data, no conclusion pertaining to the length of time required for surgery to improve severity in disordered respiration during sleep in individuals with OSA is drawn.

No studies met the inclusion criteria for this key question.

SaO_2

Individuals with OSA show significant improvement in SaO_2 during sleep after one night of CPAP treatment. (Strength of Evidence: Moderate)

Seven moderate-to-high quality studies assessed SaO_2 during sleep in individuals with OSA following CPAP treatment. These seven studies consistently demonstrated that oxygen during sleep improves following CPAP treatment.

Due to a paucity of data, no conclusion pertaining to the length of time required for medication to improve SaO_2 during sleep in individuals with OSA is drawn.

Six moderate-to-high quality studies assessed SaO_2 during sleep in individuals with OSA following treatment with a medication. These studies found that the administration of theophylline, salmeterol, or aminophylline for one day had no significant effect on any measure of SaO_2. Similarly, the administration of mirtazapine or MPA for seven days had no significant effect on any measure of SaO_2.

Due to a paucity of data, no conclusion pertaining to the length of time required for oral appliances to improve SaO_2 during sleep in individuals with OSA is drawn.

Two moderate-quality studies assessed SaO_2 during sleep in individuals with OSA following treatment with two different oral appliances. The results of these two studies were mixed. One study(214) indicated that oral appliances are effective in significantly increasing minimum SaO_2 during sleep in individuals with OSA after one week of treatment. The other study(209) reported that oral appliances did not significantly change minimum SaO_2 after one night of treatment .

Due to a paucity of data, no conclusion pertaining to the length of time required for surgery to improve SaO_2 during sleep in individuals with OSA is drawn.

No studies met the inclusion criteria for this key question.

Blood Pressure

Due to a paucity of data, no conclusion pertaining to the length of time required for CPAP to improve blood pressure in individuals with OSA is drawn.

Three moderate-quality studies (each with a different assessment period) assessed blood pressure in individuals with OSA following CPAP treatment. The results of these three studies indicate that with CPAP treatment, individuals with OSA show significant improvement in blood pressure following two weeks of treatment, but not after one night or one week of treatment.

Due to a paucity of data, no conclusion pertaining to the length of time required for theophylline to improve blood pressure in individuals with OSA is drawn.

One moderate-quality study assessed blood pressure in individuals with OSA following treatment with theophylline. This study reported that the administration of theophylline for one night had no significant effect on any measure of blood pressure.

Due to a paucity of data, no conclusion pertaining to the length of time required for oral appliances or surgery to improve blood pressure in individuals with OSA is drawn.

No studies met the inclusion criteria for this key question.

Psychomotor/Cognitive Functioning

Due to a paucity of data, no conclusion pertaining to the length of time required for CPAP to improve psychomotor and cognitive functioning in individuals with OSA is drawn.

Four moderate-to-high quality studies assessed psychomotor or cognitive functioning in individuals with OSA following CPAP treatment. The results of these four studies indicate that with CPAP treatment, individuals with OSA show significant improvement in some measures of psychomotor and cognitive functioning after as little as one night of treatment. However, most measures do not show any change after one week of treatment.

Due to a paucity of data, no conclusion pertaining to the length of time required for theophylline and modafinil to improve psychomotor and cognitive functioning in individuals with OSA is drawn.

Three moderate-to-high quality studies assessed psychomotor and cognitive functioning in individuals with OSA following treatment with either theophylline or modafinil. These studies reported that the administration of theophylline for one night significantly improved some measures of psychomotor and

cognitive functioning, but had little effect on most other measures. Furthermore, two weeks of modafinil had no significant effect on any measure of psychomotor and cognitive functioning.

Due to a paucity of data, no conclusion pertaining to the length of time required for oral appliances or surgery to improve psychomotor and cognitive functioning in individuals with OSA is drawn.

No studies met the inclusion criteria for this key question.

Key Question 7: How soon, following cessation of treatment (e.g., as a consequence of noncompliance), will individuals with OSA demonstrate reduced driver safety (as determined by crash rates or through indirect measures of crash risk)?

Given the high crash risk associated with untreated OSA (see findings of Key Question 1) and the fact that treatments such as CPAP are clearly effective in reducing this risk, it is not surprising that issues of treatment compliance are of particular concern to those charged with overseeing transportation safety. Regardless of how effective a treatment may be, if it is not applied correctly, its value in reducing crash risk will be diminished. This must be taken into account by those medical examiners who must determine whether an individual with OSA who is undergoing a treatment that is known to be effective can be considered safe to drive a CMV. While noncompliance is not an issue for individuals who have undergone surgical treatment, it is an extremely important factor for individuals who have been treated by other means.

As evidenced by Table 89, noncompliance rates for CPAP are very high. While data on compliance for other treatments are scarce, available evidence suggests that noncompliance may be less of a problem for other treatment options for OSA (such as dental appliances and medication).

Table 89. Treatment Noncompliance Rates and Reasons for Noncompliance among Individuals with OSA

Reference	Study population	Study duration	How was compliance measured?	Definition of noncompliance	% noncompliant at longest follow up	Stated reasons for noncompliance
CPAP						
Ballester et al.(164)	68 patients receiving CPAP plus conservative treatment with AHI >15 and mild to moderate symptoms. 37 patients receiving only conservative treatment.	3 months	NR	<4.5 hours/night	27%	NR
Bao et al.(202)	41 patients aged 35 – 65 years with RDI >15	1 week	Hidden compliance clock measuring amount of time CPAP unit was switched on	<5 hours/night	26% CPAP 24% Sham CPAP	NR
Barnes et al.(166)	80 middle-aged, predominantly male, (80%) overweight patients with mild to moderate OSA	1 week	Inbuilt "time at pressure" meter	<4 hours/night on at least 70% nights	57% CPAP 29% MAS (self-reported)	• Unable to tolerate CPAP (1) • Several subjects required a different mask from the one that they were initially fitted with. Changes were all resolved by week 4 of treatment. • CPAP more difficult to use versus MAS
Barnes et al.(98)	28 middle-aged, overweight patients with AHI between 5-30/hours	4 months	Built-in compliance meter	<4 hours/night	52%	• Intolerance
Brander et al.(215)	49 subjects new to CPAP	6 months	CPAP run time measured by an external clock and self-report one-month follow-up	Stopped using machine at some point during 6-month follow-up	24%	• Nasal symptoms (7) • No treatment motivation (1) • Inability to sleep with CPAP (3) • Claustrophobia (1)
Cassel et al.(78)	59 Caucasian males aged 25-65 years, licensed drivers with EDS referred to the University Hospital Marburg Sleep Disorders Clinic	12 months	Self-reported questionnaire and when available, reading the inbuilt timing-meters of CPAP device	NR Objective nightly use: 7.2.±0.16 hours Average reported nightly use: 7.2 ±0.13 h	9%	• Noisy • Machines too big • Masks need improvement
Coughlin et al.(171)	34 obese Caucasians diagnosed with OSA recruited from a sleep disordered breathing clinic; naive to CPAP, not known to suffer from other medical conditions	3 months	Measured electronically on a smartcard that was recorded as machine running time	<3.5 hours/night	32%	NR

Reference	Study population	Study duration	How was compliance measured?	Definition of noncompliance	% noncompliant at longest follow up	Stated reasons for noncompliance
Engelman et al.(172)	13 patients recruited from a sleep clinic complaining of at least 2 symptoms of SAHS and with an AHI ≥5 hours/slept during PSG	6 weeks	Hidden time clocks logging effective CPAP use	Average ≤3 hours/night	31%	NR
Engelman et al.(105)	16 consecutive patients presenting at Scottish National Sleep Laboratory with ≥2 OSA symptoms and AHI in range of 5.0-14.9 hours/slept during PSG	2 months	Reading time clocks hidden within CPAP casing that measured the total duration of treatment	<5 hours/night	50%	Patients with mild SAHS are likely to show proportionately less disturbed sleep than those with more severe SAHS and may require shorter CPAP duration to acquire enough sleep required to achieve normal daytime function
Faccenda et al.(216)	68 consecutive patients referred to a sleep center with at least 2 symptoms of SAHS and an AHI≥15 on PSG	2 months	Sullivan V Elite CPAP units were downloaded at the end of each 1-month treatment period to obtain the real-time record of time the patient was using CPAP at correct pressure	Use of CPAP <3.5 hours/night	53%	NR
George et al.(156)	17 male patients recruited from London Health Sciences Center aged 49.7 ±11.2 years	12 months	Direct questioning	High use defined as >6 hours/night for ≥six nights/wk	0%	NA
Hui et al.(179)	56 patients with moderately severe OSA and mild sleepiness	3 months	Time counter recording machine run time	<5 hours/night	43%	• General intolerance
Lindberg et al.(217)	A population-based sample of 38 men who completed a sleep questionnaire and were ultimately diagnosed with OSA	6 months	Built in timers measuring the amount of time the machine was on	Terminated treatment entirely	71%	• Problems from nose or pharynx • Inability to sleep with a mask
Lojander et al.(182)	15 OSA patients aged 18-65 years	12 months	Built in counter plus self-reports	<4 hours/night, 5 nights week	13%	• General intolerance
Lojander et al.(183)	49 (10 CPAP treated) middle-aged, moderately-obese OSA patients with EDS	12 months	Built in counter in CPAP unit	<4 hours/night, <5 nights/week	10%	NR
Monasterio et al.(187)	66 CPAP-treated patients and 56 controls with mild SAHS from 6 sleep centers in Spain	6 months	Time clocks on CPAP unit	<4 hours/night	36%	NR
Nussbaumer et al.(218)	30 patients treated with auto-adjusted and constant CPAP with EDS and AHI >10 events/hour	2 month		Use <2 hours/night	6%	• Noise from cCPAP • Discomfort from high pressure in cCPAP

Reference	Study population	Study duration	How was compliance measured?	Definition of noncompliance	% noncompliant at longest follow up	Stated reasons for noncompliance
Popescu et al.(219)	196 subjects who agreed to try CPAP at home for 2 weeks	12 months	Machine run time/number of days between readings	<2 hours/night at one year follow-up = unsatisfactory use	47%	NR
Rauscher et al.(220)	63 consecutive individuals with OSA prescribed CPAP for a minimum of 3 months	539 ±44 days	Self report and machine run time. Objective compliance = run time/number of days since initiation of treatment	<4 hours/night as measured by objective report	29%	NR
Rauscher et al.(221)	65 subjects with AHI >15 who agreed to a one night trial of CPAP	1 night	Accepted CPAP for home therapy or refused	Refusers would not continue CPAP after first night	28%	• Difficulty falling asleep with device on (15) • Frequent nocturnal awakenings (7) • Discomfort caused by the mask (5)
Reeves-Hoche et al.(222)	44 subjects new to CPAP	3 month	CPAP run time and effective pressure time were measured as machine run time/reported hours of sleep and prescribed mask time/machine run time, respectively.	CPAP failures = those not using the machine at 3 months	20%	• Nocturia (1) • Nasal bridge pressure (2) • Elected to have UPPP (2) • Declared himself cured (1) • Underwent tracheotomy (1)
Ryan et al.(195)	10 patients with history of heart failure of at least 6 months, left ventricular systolic dysfunction and AHI ≥20/hours of sleep	1 month	Metered CPAP machine to document hours of use	<6 hours/night	0%	NA
Woodson et al.(199)	90 (30 CPAP treated) patients with self-reported daytime sleepiness, and mild-moderate OSA with no prior CPAP treatment	2 months	Pressure on time was acquired from usage software within CPAP device, and self report usage was recorded at 8-week visit	<4 hours/night and <5 nights/week	62.5% objective measurement 23% subjective reporting	NR
Yamamoto et al.(89)	47 males aged 49.5 ±10.8 years with severe OSA	38.8 ±8.2	Self-report on questionnaire after 2-year use	NR	2.2%	• Discomfort from mask
Zimmerman et al.(223)	58 subjects new to CPAP with impaired memory function	3 months	Covert monitoring using an internal microprocessor housed within the device. Compliance = total number of hours at the prescribed pressure per 24 hour period.	Subjects categorized as poor compliers, less 2 hours per night; moderate users, 2-6 hours per night; and optimal users, greater than 6 hours per night	67%	NR

Reference	Study population	Study duration	How was compliance measured?	Definition of noncompliance	% noncompliant at longest follow up	Stated reasons for noncompliance
Dental Appliance						
Hoekema et al.(155)	19 patients aged 21-70 years diagnosed with OSA with AHI >5	3 months	Self-report (adjusted for by – 1 hour/night from self-reported usage)	Patients OA "adequate usage" listed as 7.0 ±0.9 hours/night for 6.8 ±0.4/nights/ week	0%	NA
Medication						
Espinoza et al.(213)	10 male patients with AHI>15 and daytime hypersomnolence	2 nights – 1 week apart	NR	Not returning for second infusion of Aminophylline	0	NA
Kingshott et al.(100)	30 sleep apneics receiving effective CPAP therapy	7 weeks	Unused tablets returned by patients were counted. Percentage compliance was calculated using this formula (tablets taken/expected tablets taken)* 100	Not taking Modafinil tablets as instructed	1%	• Headache • Nausea • Dry mouth
Pack et al.(101)	157 patients recruited from 22 U.S. centers with RDI≥15 before or in the absence of CPAP therapy, regular users of CPAP for ≥2 months with evidence of residual EDS	4 weeks	NR	Noncompliance with the drug or alcohol restriction	2%	• Noncompliance with drug or alcohol restriction (3)
Roth et al.(224)	395 patients adherent to CPAP therapy with moderate OSA and residual daytime sleepiness	3 months	Pill counts and reviews of patient diaries	Not taking Armodafinil/ Placebo tablets as instructed; Not complying with study procedures	1%	• Not taking tablets as instructed (1) • Not complying with study procedures (2)

AHI = Apnea-hypopnea index; CCPAP = Constant continuous positive airway pressure; CPAP = Continuous positive airway pressure; EDS = Excessive day-time sleepiness; MAS = Mandibular advancement splint; NA = Not applicable; NR = Not reported; OSA = Obstructive sleep apnea; PSG = Polysomnogram; RDI = Respiratory disturbance index; SAHS = Sleep apnea hypopnea syndrome; UPPP = Uvulopalatopharyngoplasty.

Predictors of Poor Compliance

While investigations into factors that predict poor compliance among individuals treated with most treatments for OSA are nonexistent, a number of investigators have attempted to determine the factors that predict poor compliance among users of CPAP. The findings of these studies are summarized below:

- Ball et al.(225) found that the most striking difference between noncompliers and compliers with CPAP was their level of satisfaction with treatment; noncompliers were much less happy with the CPAP equipment and service they received from their physicians. Lower compliance was also found to be more common among individuals with sleep hygiene disorder.
- Waldhorn et al.(226) examined the medical records of all OSA cases (n = 96) referred to a single university medical center who were treated with CPAP. Recorded data included polysomnographic information obtained from the initial overnight sleep study during which an OSA diagnosis was made and a repeat sleep study was conducted at an unspecified time point. In addition, the investigators conducted one-time telephone interviews with the individuals studied and asked them to retrospectively rate and compare the severity of their daytime sleepiness before and after treatment. At the time of the telephone interview, 76% of the 96 enrollees were still using CPAP: 5% of individuals were using the device intermittently, and the remainder (19%) had discontinued CPAP prior to survey administration. In total, 40% of noncompliers stopped using CPAP within the first two months, 66% had discontinued CPAP therapy at the 6-month point, and 87% had ceased to use it within the first year. Compliers were distinguished from noncompliers by the severity of daytime sleepiness at baseline; compliers had more severe daytime sleepiness than their noncompliant counterparts. In contrast, however, Sampol et al. did observe an association between severity of daytime sleepiness and compliance in their sample of individuals with both OSA and coronary artery disease.(227) Edinger found that severe daytime sleepiness was predictive of noncompliance rather than compliance in a sample of male war veterans.(228) Other predictors of noncompliance observed in this latter population included high BMI, low levels of depression and hypochondria, and better subjective sleep quality.
- Pelletier-Fleury et al. examined the relationship between age and compliance in a prospective cohort of individuals with OSA observed at the sleep laboratory of a Paris teaching hospital.(229) They found overall compliance after three years of CPAP use to be 67.34%. However, when those over 60 years of age were compared with younger subjects, compliance with CPAP was consistently lower at all time points assessed for the older age group. No independent effect of age was found once other variables associated with advancing age were controlled for, including sex, low ESS scores, and severity of OSA. Of 50 patients included in the study of Pelletier-Fleury who did stop treatment, their reasons included insomnia, equipment being too loud, claustrophobia, and skin lesions from the mask and nasal side effects. In comparison, individuals who remained on treatment tended to be more highly educated, more often employed in white collar professions, had more EDS, and had less ability to perform daily tasks. Among the intermittent users, those who skipped entire nights also tended to use CPAP for fewer hours on those nights on which they did apply the machine. Pelletier-Fleury et al. also found that noncompliance started very early for the intermittent users, usually commencing within the first or second week of treatment.(230)
- Bachour and Maasilta investigated adherence to CPAP in individuals with moderate to severe OSA, comparing those who were primarily mouth breathers (>70% of total sleep time) versus individuals who were primarily nose breathers.(231) The authors speculated that mouth

breathing would allow more pressure to escape and reduce CPAPs effectiveness, thereby limiting the treatment's impact on daytime symptoms and affecting the compliance levels of mouth breathers to CPAP therapy. As expected, throughout the three-month follow-up, nose breathers were significantly more compliant with treatment than mouth breathers. While both groups experienced a significant drop in the percent of time spent in mouth breathing, at the final follow-up visit, the individuals in the mouth breathing group still spent a significantly higher portion of the night mouth breathing than those assigned to the nose breathing group.

Interventions Designed to Improve Compliance

Given the threat that OSA poses to driver safety and the fact that noncompliance with nonsurgical treatments is a potential problem—especially among CPAP users—we performed a search for studies of strategies designed to improve compliance. These searches did not identify any studies pertaining to compliance improvement strategies for dental devices, behavior modification, or medications. Our searches did, however, identify several studies that examined strategies designed to improve compliance with CPAP. The strategies examined in these studies were varied, ranging from the implementation of educational or psychologic interventions to changes in the ergonomics of the device itself.

Haniffa et al. conducted a systematic review that included data from 24 RCTs of interventions designed to increase compliance with CPAP when used in the home setting.(232) Generally, the subjects enrolled in these studies had severe OSA; the majority were CPAP naive. Thirteen of the 24 included trials compared auto-titrating CPAP with fixed CPAP; three trials examined bi-level CPAP compared with fixed CPAP; one study compared patient-titrated versus fixed CPAP; one examined humidification added to fixed CPAP versus fixed CPAP alone; and the remaining six trials examined the ability of various educational/psychologic strategies to improve compliance. In another systematic review, Ayas et al. examined compliance rates associated with auto-titrating CPAP as compared to fixed CPAP.(233) In a third systematic review, Chai et al. studied the role of various interface devices on CPAP compliance.(234)

Compliance Rates: Auto-titrating CPAP versus CPAP

Whether the use of auto-titrating CPAP improves compliance when compared to regular CPAP has not been clearly demonstrated at this time. Haniffa et al. reported that the results of the studies included in their systematic review did not differ across devices.(232) The meta-analysis conducted by Ayas et al. agreed with Haniffa et al.'s finding, determining that compliance and withdrawal rates were similar for both CPAP devices.(233) Additionally, Ayas et al. reported that individuals preferred auto-titrating CPAP over fixed-CPAP.(232)

In four studies that were not included in the systematic reviews discussed above, investigators found that treatment-naïve OSA individuals demonstrated equal compliance when treated with fixed- or auto-titrating CPAP for up to eight-weeks duration.(235-239)

Compliance Rates: Bi-PAP versus CPAP

Currently available evidence does not demonstrate that the use of Bi-PAP has a positive impact on compliance and withdrawal rates when compared to CPAP.(232)

Compliance Rates: Pressure Relief CPAP versus fixed CPAP

Currently available evidence does not demonstrate that the use of Bi-PAP has a positive impact on compliance and withdrawal rates when compared to regular CPAP.(240)

Compliance Rates: Flexible CPAP versus Fixed CPAP

Limited evidence suggests that flexible CPAP may improve compliance. Aloia et al. found flexible CPAP users to be more compliant with treatment at the three-month follow-up point than those in the standard CPAP group.(241)

Compliance Rates: Humidification Therapy plus Fixed CPAP versus Fixed CPAP Alone

Currently available evidence does not demonstrate that heated humidification plus fixed CPAP has a positive impact on compliance and withdrawal rates when compared to regular CPAP.(232,242)

Compliance Rates: Fixed CPAP plus Education/Support versus Fixed CPAP Alone

The impact of the addition of education/support to fixed CPAP therapy was assessed in the systematic review of Haniffa et al.(232) The investigators reported that the addition of cognitive-behavioral therapy to CPAP may improve compliance. Overall, after 12 weeks of either cognitive behavioral therapy or feedback sessions, the group who had received cognitive-behavioral therapy was significantly more compliant. Two further trials included in the Haniffa review investigated the effect of increased device support with standard support on compliance. These studies demonstrated conflicting results: one study found that intensive support had a positive impact on compliance; the other study found no such impact. Several other studies examined by Haniffa which investigated the effect of literature, supportive phone calls, other reinforcements, and a short educational session about the device failed to demonstrate an improvement in compliance when compared with standard support.

Since the publication of the systematic review of Haniffa et al.(2004), two further studies have been published. Meurice et al. studied the impact of four different levels of education on compliance, including: standard education (oral instructions by prescriber); reinforced education (oral and written instruction); standard education by homecare network (home visit and telephone access to provider); and reinforced education by homecare team (repeated home visits).(243) All subjects enrolled in the study simultaneously received two types of education and were recruited from seven centers in the French federation of homecare associations. Compliance rates over a one-year period did not differ among groups.

A 15-minute video about OSA and CPAP led to an increase in return clinic visits compared with standard education (72.9% versus 48.9%, respectively) in a group of mild OSA sufferers studied by Wiese et al.(244) A combination of interventions that included educational videos, telephone support, and extra appointments with a sleep specialist compared with standard-of-care CPAP treatment did not produce a difference in compliance rates as measured by covert monitoring-of-machine run time. However, there was a trend over the course of the one-year follow-up for those receiving the comprehensive intervention to attend scheduled routine clinic visits.(245)

Several recently published studies have investigated the role of telemedicine in increasing compliance in CPAP users. Smith et al. (2006) studied the impact of 12 weeks of in-home telehealth services on a group of individuals with OSA who had been treated with CPAP for three months but who had proven to be noncompliant with the therapy. Both the treatment and control had a telehealth system with audio and video capabilities set up in their home for the purpose of maintaining communication between the

person with OSA and a nurse. In the control group, the focus of these interactions was on vitamin intake, while the importance of regular and proper CPAP use was discussed in the treatment group. The investigators found telehealth in-home equipment to be effective at increasing compliance, with 90% of treatment group versus 44% of the controls being compliant at follow-up. The authors note that one subject in the intervention group was a truck driver and that his work schedule caused him to miss a weekday session, which he eventually made up.(246)

DeMolles et al. conducted a pilot study of a telephone-linked communication system with 30 individuals with sleep apnea. The telephone-linked communication system acted as an educator, counselor, and at-home monitoring device, providing a system for both regular physician notification or for use in situations where noncompliance or other treatment side effects arose that required expert assistance. To use the intervention, subjects called the automated system weekly and answered questions regarding compliance. Based on the subjects' responses, they received additional support or education as needed. Investigators found that individuals who received the telephone-based support used CPAP for 4.4 ±3.0 hours per night compared with 2.9 ±2.4 for those receiving usual care. However, this difference was not statistically significant.(247) In a similar study, Taylor et al. compared usual care to usual care plus telemedicine support services in a population of military personnel and their beneficiaries. Like Des Molles et al. Taylor et al. found no benefit from adding telemedicine supportive services to the typical care received by individuals undergoing CPAP therapy.(248)

Compliance Rates: Compliance with CPAP by Type of Interface Delivery Device

Chai et al.(234) performed a systematic review of RCTs (K = 4) that compared different CPAP delivery interface devices in newly diagnosed or new-to-treatment individuals with severe OSA. Objective measures of compliance, adverse events, patient satisfaction/preference, physiologic parameters of sleep, quality of life (QOL), and symptomatology were each examined. Two of the four studies included in the review compared nasal masks with a novel oral mask (the Oracle, a strapless butterfly-shaped mask made of silicone that rests on the lips and teeth, where it functions to create a seal over the lips and cheeks and holds the tongue in place). A third trial reviewed compared nasal pillows with a nasal mask, and the fourth trial tested a nose mask versus a full face mask.

Combining data from the two studies that compared the Oracle to nasal masks, mean hours of use per night were not statistically different between study groups. Similarly, in terms of total side effects, there were no between-group differences. However, oral masks were associated with dry mouth or throat, excessive salivation, and sore lips and gums, while nasal mask wearers reported more pressure from the mask and straps, air leaks, and mask dislodgement. No statistically significant differences were found in subject preference for one type of interface over the other.(234) In the study that compared a nasal mask to nasal pillows, the percentage of days used was higher for nasal pillows, but the mean daily use and mean daily use for days with >0 minutes use was similar for both groups. However, the nasal pillow wearers reported fewer side effects, and the pillows were graded as more satisfactory than the nasal mask.(234)

Finally, the study that compared compliance rates between nose and full-face mask users found compliance in the nose mask group to be higher and for this treatment modality to be rated more comfortable by study subjects. Face mask users reported less dry throat, mouth, and nose than nasal mask users, but they experienced more air leaks, red/sore eyes, claustrophobia, and difficulty exhaling. Chai et al. concluded that face masks should not be the initial treatment given to new CPAP users; nasal pillows should be considered over nasal masks; and oral masks should have a place among individuals with OSA who cannot tolerate nasal apparatus.

Rationale for Asking Key Question 7

Given the high noncompliance rates associated with CPAP and the lifestyle of an interstate CMV driver, it is highly likely that compliance rates among this population will be very poor. Consequently, it is necessary to know what the deleterious impacts of noncompliance will be on the effectiveness of the treatment and how quickly these deleterious impacts are likely to occur.

Identification of Evidence Base

The identification pathway for the evidence base used to address Key Question 7 is summarized in Figure 48. Our searches identified a total of 185 potentially relevant articles. Of these articles, 120 were retrieved and read in full, and 4 were found to meet the inclusion criteria for this question (Table 90). Table D-7of Appendix D lists the 116 articles that were retrieved and then excluded and provides a reason for their exclusion.

Figure 48. Evidence Base Development Process

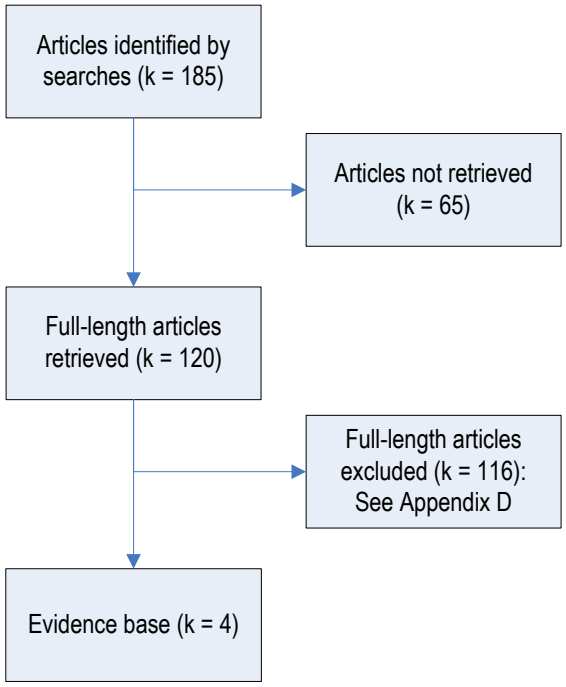


Table 90. Evidence Base

Primary Reference	Year	Study Location	Country
Nolan et al.(249)	2006	Dublin	Ireland
Turkington et al.(159)	2003	Leeds	UK
Sforza and Lugaresi(106)	1995	Bologna	Italy
Barone-Kribbs et al.(107)	1993	Pennsylvania	USA

Key Characteristics of Evidence Base

This subsection provides a brief description of the key attributes of the four included studies that met the inclusion criteria for Key Question 7. The key attributes of each of the 4 included studies that address Key Question 7 are presented in Table 91. Detailed information pertinent to this section that has been extracted from the included studies is presented in Study Summary Tables that can be found in Appendix G.

Table 91. Key Study Design Characteristics of Studies that Address Key Question 7

Reference	Year	Size	Study design	Prospective?	Study population	Aim of study	Method of measuring compliance	Measurement of OSA	Amount of time off treatment (days)
Nolan et al.(249)	2006	27	RCT (X-over)	Yes	27 subjects with severe OSA attending a single sleep disorder unit who were already established on and highly compliant with CPAP were randomized and crossed over to three different APAP machines.	To compare the effects of three APAP devices on treatment compliance, QOL and side effects in individuals with OSAS already established on fixed-pressure CPAP therapy.	Time coded compliance data from the fixed-pressure CPAP was downloaded at the start of the study and the three APAP devices were downloaded at the end of each 4 week trial.	Confirmed OSAS and already established on fixed-pressure CPAP therapy.	Subjects used each device for 4 weeks and were then retested. Subjects went from a median usage of 100% of nights to 59% of nights with the Breas Pv 10i.
Turkington et al.(159)	2003	36	Controlled Trial	Yes	18 subjects with moderate to severe SAHS were tested before, during, and after a 2-week trial of CPAP; another 18 subjects with moderate to severe SAHS were tested before receiving their 2-week CPAP trial.	To assess the time course of changes in driving simulator performance both during a 2-week trial of CPAP and after its cessation.	Internal clocks recorded CPAP run time.	Limited sleep studies using either the Autoset Clinical 1 or the Densa DMS2000.	Subjects retested 1, 3, and 7 days after cessation of therapy.
Sforza and Lugaresi(106)	1995	30	Case Series	Yes	30 patients with moderate to severe OSAS on treatment for a minimum of 1 year.	To establish the effect of chronic CPAP on subjective and objective sleepiness after at least 1 year of home therapy and to ascertain whether a worsening of daytime sleepiness appears after a single night of therapy withdrawal even in long-term treated patients.	Every six months during the home treatment period, subjects answered a self-administered questionnaire on CPAP use. Subjective compliance was determined by the reported hours of use per night and by the reported nights of use per week.	PSG	Subjects retested 1 day after cessation of therapy

Reference	Year	Size	Study design	Prospective?	Study population	Aim of study	Method of measuring compliance	Measurement of OSA	Amount of time off treatment (days)
Barone-Kribbs et al.(107)	1993	15	Case Series	Yes	Consecutive individuals with a diagnosis of apnea recruited from a university's sleep disorder center.	To determine if intermittent use of CPAP by individuals with OSA is a safe and effective strategy by evaluating the physiologic and behavioral outcomes of sleeping without CPAP for a single night following a period of regular use.	Subjects successfully used CPAP for at least 1 month (defined as use of at least 4 hours per night on 80% of the days and on at least 5 of the 7 days before returning to the lab for follow-up assessment) based on self-reported home daily diary (n = 10) and objective CPAP microprocessor monitor installed in the CPAP units (n = 5). CPAP monitor is a microprocessor located inside the CPAP machine that measured actual pressure at the mask every minute of each 24 hour day during the study period. The microprocessor was programmed to detect when the mask was on (pressure above a preset threshold) so that the actual nightly use was determined.	PSG demonstrating an RDI of at least 15 events/hour and the next day an MSLT of less than 10 minutes	Subjects retested 1 day after cessation of therapy

APAP = Automatic positive airway pressure; CPAP = Continuous positive airway pressure; MSLT = Multiple sleep latency test; OSA = Obstructive sleep apnea; OSAS = Obstructive sleep apnea syndrome; PSG = Polysomnogram; QOL = Quality of life; RCT = Randomized controlled trial; RDI = Respiratory disturbance index; SAHS = Sleep apnea hypopnea syndrome.

All four included studies examined how rapidly CPAP therapy cessation would impact outcomes known to be associated with an increased crash risk (simulated driving performance, 1 study; increased severity of OSA and daytime sleepiness, 4 studies).

Turkington et al.(159) measured driving simulator performance and subjective daytime sleepiness in OSA subjects before, during, and after a two-week trial of CPAP. Sforza and Lugaresi(106) and Barone-Kribbs et al.(107) studied the effects of a single night of CPAP withdrawal on both objective and subjective measures of sleepiness in individuals with OSA. Subjects in the Sforza and Lugaresi trial utilized CPAP for a minimum of one year before cessation of treatment, while the Barone-Kribbs et al. participants utilized CPAP for a single month prior to treatment removal. Nolan et al. compared three different auto-titrating CPAP machines in terms of treatment compliance, side effects, and QOL in compliant subjects already using fixed CPAP therapy. All four included studies were small; the largest study enrolled a total of 36 individuals with OSA. All trials were conducted prospectively.

Study follow-up lengths varied from three weeks to one full year. Sforza and Lugaresi(106) conducted PSG on subjects prior to one year of at-home use of CPAP. During this one-year period, subjects completed two self-administered questionnaires at six-month intervals regarding the frequency of their CPAP use. Like Sforza and Lugaresi, Barone-Kribbs et al.(107) administered a PSG to subjects and then instituted at-home CPAP use. Barone-Kribbs' subjects were required to use CPAP at home for one month before returning for a second in-laboratory evaluation. Nolan et al.(249) identified subjects already established on CPAP and then brought them in for a 12-week trial, comparing three different auto-titrated CPAP machines for 4 weeks each. Turkington et al.(159) followed their study participants for only three weeks; two weeks using CPAP and the last week without treatment.

Generalizability of Evidence Base to CMV Driver Population

Important characteristics of the individuals with OSA enrolled in the studies included in the evidence base for Key Question 7 are presented in Table 92.

Table 92. Characteristics of Patient Enrolled in Studies that Address Key Question 7

Study	n =	% male	Age	BMI	Severity of apnea	Treatment	Duration of Treatment	Amount of Treatment per Night (hours)	% CMV Drivers	Generalizability to CMV Drivers
Turkington et al.(159)	18	94	Mean = 49.9 (SD) = 10	Mean = 39kg/m^2 (SD) = 7.7	RDI (events/hour) Mean = 59.8 (SD) = 16.9	CPAP	2 weeks	Mean = 4.9 (SD) = 1.5	NR	Unknown
	18	94	Mean = 51.7 (SD) = 12.2	Mean = 36.6kg/m^2 (SD) = 5.3	RDI (events/hour) Mean = 58.3 (SD) = 15.7	No treatment	NA	NA	NR	Unknown
Nolan et al.(249)	27	92.6	Median = 53 Interquartile Range = 48-67	Median = 36.2 kg-m^{-2} Interquartile Range = 31.3-38.6 kg-m^{-2}	AHI events –h $^{-1}$ Median = 48 Interquartile Range = 29-76	CPAP	Months Median = 53 Interquartile Range = 37-85	Median = 6.6 Interquartile Range = 5.9-7.9	NR	Unknown
Sforza and Lugaresi(106)	30	93.3	Mean = 47.7 (SD) = 2.1 Range: 19-66	Mean = 33.3 (kg/m^2) (SEM) = 0.7 (kg/m^2) Range:25.4-40.8(kg/m^2)	AHI (events/hour) Mean = 74.4 (SEM) = 3.0	CPAP	Days Mean = 389 (SD)=24	Mean = 6.2 Range = 2-7	NR	Unknown
Barone-Kribbs(107)	15	93.3	Mean = 45.9 (SD) = 9.0	Mean = 36.8 (SD) = 8.2	RDI Mean = 56.6 (SD) = 24.8	CPAP	Days Mean = 75.8 (SD) = 50.8 Range = 30-237	Mean = 5.7 (SD) = 1.1	NR	Unknown

AHI = Apnea-hypopnea index; BMI = Body mass index; CMV = Commercial motor vehicle; CPAP = Continuous positive airway pressure; NA = Not applicable; NR = Not reported; RDI = Respiratory disturbance index; SD = Standard deviation; SEM = Standard error of the mean.

None of the studies included in the evidence base for Key Question 7 examined the effects of OSA treatment cessation in a group of CMV drivers. Also, the degree to which the findings of the four included studies can be generalized to CMV drivers is unclear. The study populations in two of the four included studies, Turkington et al.(159) and Sforza and Lugaresi(106), consisted of individuals with moderate-to-severe OSA, while the Nolan et al. study included only severe apnea cases. The Barone-Kribbs et al.(107) study attempted to recruit individuals with "a measureable level of sleep-disordered breathing but with some level of sleepiness" and a prescription for CPAP to maximize the likelihood that changes would be observed over the course of the study. In keeping with the typical demographics of individuals with OSA, all four trials included a high percentage of middle-aged male subjects. This demographic is similar to that of the CMV driver population. All four studies reported the BMI as a measure of study participant weight. BMIs in all four studies suggest that the participants were, in general, obese, with a low mean BMI of 33.3 ±0.7 to a high of 39.0 ±7.7 kg/m^2.

Subjects in the CPAP treatment arm of the Turkington et al.(159) study used CPAP for two weeks before a seven-day withdrawal period. The median CPAP usage for the participants in the Nolan et al. study was 53 months, while the Sforza and Lugaresi(106) and Barone-Kribbs et al.(107) subjects used CPAP for a mean of 389 ±24 days (or 1.07 months) and 75.8 ±50.8 days (2.45 months), respectively. Average CPAP usage per night was 4.9 ±1.5 hours in the Turkington et al. comparative trial; 6.2 hours in the Sforza and Lugaresi trial; and 5.7 ±1.2 in the Barone-Kribbs et al. trial.(107) The median usage per night among Nolan et al. study subjects was 6.6 hours, a rate indicative of fairly high compliance.

Quality of the Evidence

The results of our analysis of the overall quality of the evidence base for Key Question 7 are presented in Table 93. This assessment found that the quality of all of the included studies was moderate. Although two of the studies, Sforza and Lugaresi and Barone-Kribbs et al. received scores of 9 or greater, both were case-series reports (which do not include a control group). The lack of a control group makes interpreting results challenging, since something other than the treatment could have brought about the change at follow-up. Therefore, noncontrolled trials cannot be graded as high quality. The other two trials, Turkington et al.(159) and Nolan et al.(249), were controlled trials, but each received a quality score that placed them in the moderate range. The Turkington et al.(159) trial did not specify if it was randomized or not. This lack of randomization of groups is problematic, because randomization helps to ensure that subjects in each study arm are comparable on baseline characteristics that may influence their response to the treatments/testing being investigated. In addition, both Turkington et al.(159) and Nolan et al. were downgraded for not blinding subjects to the treatment they received, which may have led to a placebo effect in favor of the fixed CPAP therapy condition. Rather than use no treatment group, as was done in Turkington et al.(159) the Nolan et al.(249) study investigators could have used a CPAP machine at ineffective pressure to minimize this effect and strengthen the study design.

Table 93. Quality of Included Studies

Reference	Year	Quality Scale Used	Quality
Turkington et al(159)	2003	ECRI Institute Assessment Tool for Controlled Interventional Studies that have Independent Groups	**Moderate**
Nolan et al.(249)	2006	ECRI Institute Assessment Tool for Controlled Interventional-Crossover Studies that have Independent Groups	**Moderate**
Sforza and Lugaresi(106)	1995	ECRI Institute Quality Checklist for Before-After Studies	**Moderate**
Barone-Kribbs et al.(107)	1993	ECRI Institute Quality Checklist for Before-After Studies	**Moderate**

Results

Effects of Cessation of CPAP on Simulated Driving Performance

As stated above, one included study examined the effects of CPAP cessation on simulated performance (Table 94). In a controlled trial, Turkington et al.(159) compared simulated driving performance of individuals with OSA who were treated with CPAP for a period of seven days versus individuals who were not treated with CPAP. Simulated driving performance was assessed at baseline, following seven days of treatment, and finally, seven days after treatment cessation.

Table 94. Simulated Driving Performance

Study	Year	n =	Findings	Findings
Turkington et al.(159)	2003	18 with CPAP 18 no CPAP	*Baseline* *Tracking time* p = 0.606 for CPAP versus control *Reaction time* p = 0.389 for CPAP versus control *Off-road events* p = 0.719 for CPAP versus control *7 days on CPAP:* *Tracking time* p = 0.004 for CPAP versus control *Reaction time* p = 0.036 for CPAP versus control *Off- road events* p = 0.032 for CPAP versus control *7 days off CPAP:* *Tracking time* p = 0.025 for CPAP versus control *Reaction time* p = 0.043 for CPAP versus control *Off- road events* p = 0.05 for CPAP versus control	At baseline both groups were similar on driving performance; however, once CPAP was initiated, those receiving treatment significantly outperformed those not receiving treatment. After a 7-day withdrawal of CPAP, the performance of those who had been on CPAP deteriorated but was still significantly better than performance among the no treatment group.

CPAP = Continuous positive airway pressure.

At baseline, both study groups demonstrated similar, poor driving performance. As expected, those individuals who received CPAP significantly outperformed those not receiving treatment after seven days. Following a seven-day treatment withdrawal period, the performance of those who had been treated with CPAP deteriorated markedly. Their simulated driving performance, however, was still significantly better than that observed in the control group.

Effects of Cessation of CPAP on Risk Factors for Crash

All four of the included studies evaluated the impact of CPAP withdrawal on sleepiness, and one included study evaluated the temporal impact of CPAP withdrawal on OSA severity (Table 95). Barone-Kribbs et al. examined the RDI before initiation of CPAP, following a four-week trial of CPAP and after one night without the device. They found that while one night without CPAP resulted in an increase in the RDI, the withdrawal condition was still significantly better than pretreatment scores. The finding suggested that the benefit of treatment was abating, with some lingering benefit remaining.

Subjective EDS was measured in three of the four included studies using the SSS and in the fourth study with the ESS. Using the SSS, Turkington et al.(159) found that subjective EDS returned to baseline levels after CPAP was withdrawn for a period of seven days following a two-week trial of the device. Neither Sforza and Lugaresi(106) nor Barone-Kribbs et al.(107) found a change in perceived daytime sleepiness among their subjects after CPAP was removed for a single night. However, when daytime sleepiness was measured objectively using the MSLT, Sforza and Lugaresi(106) found that one night of withdrawal from CPAP reduced the amount of time before subjects fell asleep during daytime hours. Their study did, however, demonstrate that some lingering benefit of CPAP therapy remained. Barone-Kribbs et al.(107) however, found that one night without CPAP completely reversed all of the benefits of CPAP treatment, with MSLT scores taken only one day after treatment cessation resembling their pretreatment values.

Using the ESS, Nolan et al.(249) did not find a change in subjective sleepiness from the fixed CPAP to Breas PV 10i APAP condition. A change was not found despite the fact that participants who had been utilizing CPAP and were CPAP compliant for over three years went from a median use rate of 100% of nights on CPAP to only 59% of nights using the Breas PV 10i (an autotitrating CPAP unit).

Table 95. Indirect Measures of Crash Risk

Study	Year	n=	Findings	Findings
Turkington et al.(159)	2003	18	<u>SSS</u> *Baseline:* Median = 3; (IQR) = 2-4 *Day 3 on CPAP*: Median = 2; (IQR) = 2-3 *Day 7 off CPAP*: Median = 3; (IQR) = 2-4	Subjective measures of hypersomnolence significantly improved in the treated individuals from baseline to day 3 with CPAP (p = 0.004). After seven days without CPAP, SSS returned to baseline levels as compared with the on-CPAP visit (p = 0.05).
Nolan et al.(249)	2006	27	ESS Baseline: Median = 5; Interquartile Range = 3-11 Breas Pv 10i follow-up ESS: NR	No statistically significant change in ESS with CPAP versus four weeks of treatment with Breas Pv 10i.
Sforza and Lugaresi(106)	1995	30	<u>*ESS*</u> Baseline: Mean = 2.9; (SEM: 0.2) End of Follow-up with CPAP: Mean = 1.5; (SEM: 0.1) Off CPAP: Mean = 1.8; (SEM: 0.1) <u>*MSLT (minutes)*</u> Baseline: Mean = 3.1; (SEM: 0.3) End of Follow-up with CPAP: Mean = 9.8; (SEM: 1.0) Off CPAP: Mean = 5.3; (SEM: 0.6)	The withdrawal of therapy partially reversed the improvement in MSLT. Comparing MSLT after CPAP withdrawal to MSLT just before withdrawal, the average sleep latency abruptly fell from 9.8 to 5.3 minutes even though subjects did not report significant changes in subjective alertness (ESS Mean = 1.8 ±0.1) . The average sleep latency, however, was higher than at baseline (p = 0.001).
Barone-Kribbs et al(107)	1993	15	<u>*RDI*</u> Baseline: Mean = 56.6 (SD: 24.8) Difference between Pretreatment and On CPAP: Mean = -54.1 (SD: 23.3) Difference between On CPAP and Off CPAP: Mean = 34.3 (SD: 26.7) Difference between Pretreatment to Off CPAP RDI: Mean = -19.8 (SD: 19.7) <u>*MSLT*</u> Baseline: Mn = 3.1 (SD: 2.0) Difference between Pretreatment and On CPAP: Mean = 2.4 (SD: 3.6) Difference between On CPAP and Off CPAP: Mean = -2.8 (SD: 2.3) Difference between Pretreatment to Off CPAP: Mean = -0.3 (SD=2.3) <u>*ESS*</u> Baseline: Mean = 3.5 (SD: 1.3) Difference between Pretreatment and On CPAP: Mean = -0.8 (SD: 1.0) Difference between On CPAP and Off CPAP: Mean = -0.8 (SD: 1.1) Difference between Pretreatment to Off CPAP: Mean = 0.1 (SD:1.5)	<u>*RDI*</u>: On CPAP, apneas and hypopnea were virtually eliminated (Mean = 2.5 events/hour), but one night of withdrawal led to RDI returning to a clinically treatable level (Mean = 36.8 events/hour). However, even after CPAP withdrawal, RDI was significantly less than that found before treatment. p <0.0001. <u>*MSLT*</u>: Withdrawing CPAP resulted in a significant reduction in daytime sleep latency from 5.6 to 2.8 minutes, not significantly different from the pretreatment value. p = 0.0012. <u>*ESS*</u>: No significant difference between On and Off CPAP measurements after Bonferroni correction (p = 0.0179). Generally, withdrawal of CPAP for one night may place patients at risk for daytime hypersomnolence similar to their pretreatment level.

CPAP = Continuous positive airway pressure; ESS = Epworth sleepiness scale; IQR = Interquartile range; MSLT = Multiple sleep latency test; NR = Not reported; RDI = Respiratory disturbance index ; SD = Standard deviation; SEM = Standard error of mean; SSS = Stanford sleepiness scale.

Conclusions

Cessation of CPAP leads to a decrease in simulated driving ability and increases in both OSA severity and daytime sleepiness. The rate at which this deterioration occurs cannot be determined; however, this deterioration may occur as soon as 24 hours following cessation of treatment (Strength of Evidence: Acceptable).

A total of four studies met the inclusion criteria for Key Question 7 (Overall Quality of Evidence Base: Moderate). All four included studies assessed the effects of withdrawal from CPAP. None of the included studies addressed assessed the effects of cessation of CPAP treatment on increased actual crash risk following cessation of OSA treatment. However, one of the four included studies investigated the effects of withdrawal of CPAP on simulated driving performance. Turkington et al.(159) found that simulated driving performance began to deteriorate within seven days of treatment cessation. The magnitude of this deterioration was not such that driving performance had reached its pretreatment levels.

Measures of subjective daytime sleepiness appeared to be unaffected in both studies that removed CPAP for one day. Likewise, the Nolan et al.(249) study, which switched highly compliant, fixed CPAP users to an APAP device that reduced their compliance to just over half its previous level, did not find a change in subjective measures of sleepiness either. Assessment of more objective measures of daytime sleepiness (as measured using the MSLT) found that one night without CPAP led to shorter daytime sleep latency periods. In subjects who had been treated with CPAP for a minimum of four weeks, the benefits of CPAP were completely reversed after one night without the device, while subjects who had been on CPAP for a full year still experienced some lingering treatment effect. However, in subjects who have CPAP removed for an entire week, perceived sleepiness returns following treatment withdrawal.

Severity of OSA as measured by RDI shows that one night off CPAP led to a return in disease severity, which was significant but not enough to return subjects to their pretreatment level. The impact of longer withdrawal periods on RDI is not known. However, an increase in disease severity and a return of sleepiness by objective measures suggests that withdrawal of treatment for even a short period is deleterious to individuals with OSA, even though it may take some time before they perceive these changes.

Bibliography

1. Shadish WR, Haddock CK. Combining estimates of effect size. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 261-77.
2. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998 Dec 30;17(24):2815-34.
3. Hedges LV. Fixed effects models. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 285-99.
4. Raudenbush SW. Random effects models. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 301-21.
5. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. Psychol Methods 1998;3(4):486-504.
6. Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. Pain 2000 Apr;85(3):415-24.
7. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol 1999 Jul 15;150(2):206-15.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002 Jun 15;21(11):1539-58.
9. Conti CR. Clinical decision making using cumulative meta-analysis [editorial]. Clin Cardiol 1993 Mar;16(3):167-8.
10. Mottola CA. Assessing and enhancing reliability. Decubitus 1992 Nov;5(6):42-4.
11. Sterne J. sbe22: Cumulative meta-analysis. Stata Technical Bulletin 1998;42:13-6.
12. Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000 Jun 10;320(7249):1574-7.
13. Duval S, Tweedie R. Practical estimates of the effect of publication bias in meta-analysis. Australasian Epidemiologist 1998;5:14-7.
14. Duval SJ, Tweedie RL. A non-parametric 'trim and fill' method of assessing publication bias in meta-analysis. J Am Stat Assoc 2000 Mar;95(449):89-98.
15. Kiely JL, Delahunty C, Matthews S, McNicholas WT. Comparison of a limited computerized diagnostic system (ResCare Autoset) with polysomnography in the diagnosis of obstructive sleep apnoea syndrome. Eur Respir J 1996 Nov;9(11):2360-4.
16. Reichert JA, Bloch DA, Cundiff E, Votteri BA. Comparison of the NovaSom QSG, a new sleep apnea home-diagnostic system, and polysomnography. Sleep Med 2003 May;4(3):213-8.
17. Parra O, Garcia-Esclasans N, Montserrat JM, Eroles LG, Ruiz J, Lopez JA, Guerra JM, Sopena JJ. Should patients with sleep apnoea/hypopnoea syndrome be diagnosed and managed on the basis of home sleep studies? Eur Respir J 1997;10(8):1720-4.
18. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002 May 1;165(9):1217-39.
19. Aboussouan LS, Golish JA, Wood BG. Obstructive sleep apnea: warding off the sometimes dire consequences. Postgrad Med 1994;96(3):115-23.
20. Caples SM, Gami AS, Somers VK. Obstructive sleep apnea. Ann Intern Med 2005 Feb 1;142(3):187-97.
21. Lughmani NA. Sleep disordered breathing. Adv Stud Med 2003;3(6).
22. Carswell JJ, Koenig SM. Obstructive sleep apnea: Part I. Pathophysiology, diagnosis, and medical management. J Long Term Eff Med Implants 2004;14(3):167-76.

23. Hartenbaum N, Collop N, Rosen IM, Phillips B, George CF, Rowley JA, Freedman N, Weaver TE, Gurubhagavatula I, Strohl K, Leaman HM, Moffitt GL, Rosekind MR. Sleep apnea and commercial motor vehicle operators: statement from the joint Task Force of the American College of Chest Physicians, American College of Occupational and Environmental Medicine, and the National Sleep Foundation. J Occup Environ Med 2006 Sep;48(9 Suppl):S4-37.

24. Cistulli PA, Grunstein RR. Medical devices for the diagnosis and treatment of obstructive sleep apnea. Expert Rev Med Devices 2005;2(6):749-63.

25. Chervin RD, Murman DL, Malow BA, Totten V. Cost-utility of three approaches to the diagnosis of sleep apnea: polysomnography, home testing, and empirical therapy. Ann Intern Med 1999 Mar 16;130(6):496-505.

26. Hamilton WL. Can's sleep? Read this. N Y Times 2006 Apr 2; 1712 words.

27. Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of obstructive sleep apnea in adults. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007 Mar. 55 p.

28. Flemons WW, Littner MR, Rowley JA, Gay P, Anderson WM, Hudgel DW, McEvoy RD, Loube DI. Home diagnosis of sleep apnea: a systematic review of the literature. An evidence review cosponsored by the American Academy of Sleep Medicine, the American College of Chest Physicians, and the American Thoracic Society. Chest 2003 Oct;124(4):1543-79.

29. Worsnop C, Pierce R, McEvoy RD. Obstructive sleep apnoea. Aust N Z J Med 1998 Aug;28(4):421-7.

30. McNicholas WT, Krieger J, Levy P, De Backer W, Douglas N, Marrone O, Montserrat J, Peter JH, Rodenstein D. Public health and medicolegal implications of sleep apnoea. Eur Respir J 2002 Dec 1;20(6):1594-609.

31. Douglas NJ. Recent advances in the obstructive sleep Apnoea/Hypopnoea syndrome. Ann Acad Med Singapore 2002;31(6):697-701.

32. Julia-Serda G, Perez-Pen~ate G, Saavedra-Santana P, Ponce-Gonzalez M, Valencia-Gallardo JM, Rodriguez-Delgado R, Cabrera-Navarro P. Usefulness of cephalometry in sparing polysomnography of patients with suspected obstructive sleep apnea. Sleep Breath 2006;10(4):181-7.

33. Kushida CA, Efron B, Guilleminault C. A predictive morphometric model for the obstructive sleep apnea syndrome. Ann Intern Med 1997 Oct 15;127(8 Pt 1):581-7.

34. Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. J Allergy Clin Immunol 1997 Feb;99(2):S750-6.

35. Ruggles K, Hausman N. Evaluation of excessive daytime sleepiness. WMJ 2003;102(1):21-4.

36. Souza JC, Paiva T, Reimao R. Sleep habits, sleepiness and accidents among truck drivers. Arq Neuropsiquiatr 2005 Dec;63(4):925-30.

37. Canani SF, John AB, Raymundi MG, Schonwald S, Menna Barreto SS. Prevalence of sleepiness in a group of Brazilian lorry drivers. Public Health 2005 Oct;119(10):925-9.

38. Connor J, Norton R, Ameratunga S, Robinson E, Civil I, Dunn R, Bailey J, Jackson R. Driver sleepiness and risk of serious injury to car occupants: population based case control study. BMJ 2002 May 11;324(7346):1125.

39. George CF. Sleep. 5: Driving and automobile crashes in patients with obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004 Sep;59(9):804-7.

40. Stutts JC, Wilkins JW, Scott Osberg J, Vaughn BV. Driver risk factors for sleep-related crashes. Accid Anal Prev 2003 May;35(3):321-31.

41. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. Sleep - Europe 1996 Feb;19(2):156-77.

42. Berry RB, Parish JM, Hartse KM. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea. An American Academy of Sleep Medicine review. Sleep 2002 Mar 15;25(2):148-73.

43. Ng A, Gotsopoulos H, Darendeliler AM, Cistulli PA. Oral appliance therapy for obstructive sleep apnea. Treat Respir Med 2005;4(6):409-22.

44. Schmidt-Nowara W, Lowe A, Wiegand L, Cartwright R, Perez-Guerra F, Menn S. Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. Sleep - Europe 1995 Jul;18(6):501-10.

45. Wada K, Sasaki T, Jitsuiki H, Yoshimura Y, Erabi H, Hada Y, Yamashita M. Manic/hypomanic switch during acute antidepressant treatment for unipolar depression. J Clin Psychopharmacol 2006 Oct;26(5):512-5.

46. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea (Review). In: Cochrane Database of Systematic Reviews [database online]. Issue 4. Hoboken (NJ): John Wiley & Sons, Ltd.; 2005 [accessed 2007 Mar 6]. [Art. No.: CD001004]. Available: DOI: 10.1002/14651858.CD001004.pub2.

47. Pack AI, Maislin G, Staley B, Pack FM, Rogers WC, George CF, Dinges DF. Impaired Performance in Commercial Drivers: Role of Sleep Apnea and Short Sleep Duration. Am J Respir Crit Care Med 2006 May 11;174(4):446-54.

48. Howard ME, Desai AV, Grunstein RR, Hukins C, Armstrong JG, Joffe D, Swann P, Campbell DA, Pierce RJ. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med 2004 Nov 1;170(9):1014-21.

49. Treadwell JT, Tregear SJ, Reston JT, Turkelson CM. A system for rating the stability and strength of medical evidence. BMC Med Res Methodol 2006 Oct 19;6:52. Also available: http://www.biomedcentral.com/1471-2288/6/52.

50. Sutton AJ, Abrams KR, Jones DR, Sheldon T, Song F, editors. Methods for meta-analysis in medical research. John Wiley & Sons; 2001 Jan. 274 p. (Wiley series in probability and mathematical statistics).

51. Fleiss JL. Measures of effect size for categorical data. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York: Russell Sage Foundation; 1994. p. 245-60.

52. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993 Jul 30;12(14):1293-316.

53. Littenberg B, Moses LE. Estimating diagnostic accuracy from multiple conflicting reports: a new meta-analytic method. Med Decis Making 1993 Oct-Dec;13(4):313-21.

54. Mitchell MD. Sensitivity/specificity at mean threshold: a convenient description of summary ROC results [abstract no. 263]. In: 14th Annual Meeting of the International Society of Technology Assessment in Health Care; June 7-10, 1998; Ottawa, Ontario, Canada. 1998 Jun 7. p 98.

55. Greenhouse JB, Iyengar S. Sensitivity analysis and diagnostics. In: Cooper H, Hedges LV, editors. The handbook of research synthesis. New York: Russell Sage Foundation; 1994. p. 383-409.

56. Petitti DB. Approaches to heterogeneity in meta-analysis. Stat Med 2001 Dec 15;20(23):3625-33.

57. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003 Sep 6;327(7414):557-60.

58. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002 Feb 28;21(4):589-624.

59. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002 Jun 15;21(11):1559-73.

60. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004 Jun 15;23(11):1663-82.

61. Olkin I. Diagnostic statistical procedures in medical meta-analysis. Stat Med 1999 Sep 15;18(17-18):2331-41.

62. Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. J Clin Epidemiol 1995 Jan;48(1):45-57; 59-60.

63. Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. J Clin Epidemiol 1999 Apr;52(4):281-91.

64. Ioannidis J, Lau J. Evolution of treatment effects over time: empirical insight from recursive cumulative meta-analyses. Proc Natl Acad Sci U S A 2001;98:831-6.

65. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000 Jun;56(2):455-63.

66. Cooper H, Hedges LV, editors. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. 573 p.

67. Stoohs RA, Guilleminault C, Itoi A, Dement WC. Traffic accidents in commercial long-haul truck drivers: the influence of sleep-disordered breathing and obesity. Sleep 1994 Oct;17(7):619-23.

68. Barbe F, Sunyer J, de la Pena A, Pericas J, Mayoralas LR, Anto JM, Agusti AG. Effect of continuous positive airway pressure on the risk of road accidents in sleep apnea patients. Respiration 2007;74(1):44-9. Epub 2006 Jun 26.

69. Kingshott RN, Cowan JO, Jones DR, Flannery EM, Smith AD, Herbison GP, Taylor DR. The role of sleep-disordered breathing, daytime sleepiness, and impaired performance in motor vehicle crashes-a case control study. Sleep Breath 2004 Jun;8(2):61-72.

70. Pradeep Kumar VG, Bhatia M, Tripathi M, Srivastava AK, Jain S. Obstructive sleep apnoea: a case-controlled study. Neurol India 2003;51(4):497-9.

71. Shiomi T, Arita AT, Sasanabe R, Banno K, Yamakawa H, Hasegawa R, Ozeki K, Okada M, Ito A. Falling asleep while driving and automobile accidents among patients with obstructive sleep apnea-hypopnea syndrome. Psychiatry Clin Neurosci 2002 Jun;56(3):333-4.

72. Findley L, Smith C, Hooper J, Dineen M, Suratt PM. Treatment with nasal CPAP decreases automobile accidents in patients with sleep apnea. Am J Respir Crit Care Med 2000 Mar;161(3 Pt 1):857-9.

73. Horstmann S, Hess CW, Bassetti C, Gugger M, Mathis J. Sleepiness-related accidents in sleep apnea patients. Sleep 2000 May 1;23(3):383-9.

74. Lloberes P, Levy G, Descals C, Sampol G, Roca A, Sagales T, de la Calzada MD. Self-reported sleepiness while driving as a risk factor for traffic accidents in patients with obstructive sleep apnoea syndrome and in non-apnoeic snorers. Respir Med 2000 Oct;94(10):971-6.

75. George CF, Smiley A. Sleep apnea & automobile crashes. Sleep 1999 Sep 15;22(6):790-5.

76. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 1999 Mar 18;340(11):847-51.

77. Young T, Blustein J, Finn L, Palta M. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep 1997 Aug;20(8):608-13.

78. Cassel W, Ploch T, Becker C, Dugnus D, Peter JH, von Wichert P. Risk of traffic accidents in patients with sleep-disordered breathing: reduction with nasal CPAP. Eur Respir J 1996 Dec;9(12):2606-11.

79. Wu H, Yan-Go F. Self-reported automobile accidents involving patients with obstructive sleep apnea. Neurology 1996 May;46(5):1254-7.

80. Haraldsson PO, Carenfelt C, Diderichsen F, Nygren A, Tingvall C. Clinical symptoms of sleep apnea syndrome and automobile accidents. ORL J Otorhinolaryngol Relat Spec 1990;52(1):57-62.

81. Aldrich MS. Automobile accidents in patients with sleep disorders. Sleep - Europe 1989 Dec;12(6):487-94.

82. Findley LJ, Unverzagt ME, Suratt PM. Automobile accidents involving patients with obstructive sleep apnea. Am Rev Respir Dis 1988 Aug;138(2):337-40.

83. Maislin G, Pack AI, Kribbs NB, Smith PL, Schwartz AR, Kline LR, Schwab RJ, Dinges DF. A survey screen for prediction of apnea. Sleep 1995 Apr;18(3):158-66.

84. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep - Europe 1991 Dec;14(6):540-5.

85. Miletin MS, Hanly PJ. Measurement properties of the Epworth sleepiness scale. Sleep Med 2003;4(3):195-9.

86. Chervin RD, Aldrich MS. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. Neurology 1999 Jan 1;52(1):125-31.

87. Standards of Practice Committee, Adler DG, Qureshi W, Davila R, Gan SI, Lichtenstein D, Rajan E, Shen B, Zuckerman MJ, Fanelli RD, Van Guilder T, Baron TH. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc 2006 Dec;64(6):849-54.

88. Turkington PM, Sircar M, Allgar V, Elliott MW. Relationship between obstructive sleep apnoea, driving simulator performance, and risk of road traffic accidents. Thorax 2001 Oct;56(10):800-5.

89. Yamamoto H, Akashiba T, Kosaka N, Ito D, Horie T. Long-term effects nasal continuous positive airway pressure on daytime sleepiness, mood and traffic accidents in patients with obstructive sleep apnoea. Respir Med 2000 Jan;94(1):87-90.

90. Barbe, Pericas J, Munoz A, Findley L, Anto JM, Agusti AG. Automobile accidents in patients with sleep apnea syndrome. An epidemiological and mechanistic study. Am J Respir Crit Care Med 1998 Jul;158(1):18-22.

91. Noda A, Yagi T, Yokota M, Kayukawa Y, Ohta T, Okada T. Daytime sleepiness and automobile accidents in patients with obstructive sleep apnea syndrome. Psychiatry Clin Neurosci 1998 Apr;52(2):221-2.

92. Engleman HM, Asgari-Jirhandeh N, McLeod AL, Ramsay CF, Deary IJ, Douglas NJ. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. Chest 1996 Jun;109(6):1470-6.

93. Toma M, McAlister FA, Ezekowitz J, Kimber S, Gulamhusein S, Pantano A, Sivakumaran S, Cujec B, Paterson I, Armstrong PW. Proportion of patients followed in a specialized heart failure clinic needing an implantable cardioverter defibrillator as determined by applying different trial eligibility criteria. Am J Cardiol 2006 Mar 15;97(6):882-5.

94. Guilleminault C, Partinen M, Quera-Salva MA, Hayes B, Dement WC, Nino-Murcia G. Determinants of daytime sleepiness in obstructive sleep apnea. Chest 1988 Jul;94(1):32-7.

95. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. J Appl Physiol 2005 Oct;99(4):1592-9.

96. Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. Sleep - Europe 1996 Feb;19(2):104-15.

97. Haines KL, Nelson LG, Gonzalez R, Torrella T, Martin T, Kandil A, Dragotti R, Anderson WM, Gallagher SF, Murr MM. Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea. Surgery 2007 Mar;141(3):354-8.

98. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, Trinder J, Saunders NA, Douglas McEvoy R, Pierce RJ. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med 2002 Mar 15;165(6):773-80.

99. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, Monasterio C, Bosch M, Ladaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas NJ, Agusti AG. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. Ann Intern Med 2001 Jun 5;134(11):1015-23, I16.

100. Kingshott RN, Vennelle M, Coleman EL, Engleman HM, Mackay TW, Douglas NJ. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 2001 Mar;163(4):918-23.

101. Pack AI, Black JE, Schwartz JR, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. Am J Respir Crit Care Med 2001 Nov 1;164(9):1675-81.

102. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest 2000 Aug;118(2):372-9.

103. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. Am J Respir Crit Care Med 1999 Feb;159(2):461-7.

104. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. Thorax 1998 May;53(5):341-5.

105. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax 1997 Feb;52(2):114-9.

106. Sforza E, Lugaresi E. Daytime sleepiness and nasal continuous positive airway pressure therapy in obstructive sleep apnea syndrome patients: effects of chronic treatment and 1-night therapy withdrawal. Sleep - Europe 1995 Apr;18(3):195-201.

107. Kribbs NB, Pack AI, Kline LR, Getsy JE, Schuett JS, Henry JN, Maislin G, Dinges DF. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis 1993 May;147(5):1162-8.

108. Furuta H, Kaneda R, Kosaka K, Arai H, Sano J, Koshino Y. Epworth Sleepiness Scale and sleep studies in patients with obstructive sleep apnea syndrome. Psychiatry Clin Neurosci 1999 Apr;53(2):301-2.

109. Engleman HM, Hirst WS, Douglas NJ. Under reporting of sleepiness and driving impairment in patients with sleep apnoea/hypopnoea syndrome. J Sleep Res 1997 Dec;6(4):272-5.

110. Kingshott RN, Sime PJ, Engleman HM, Douglas NJ. Self assessment of daytime sleepiness: patient versus partner. Thorax 1995 Sep;50(9):994-5.

111. Verse T, Pirsig W, Junge-Hulsing B, Kroker B. Validation of the POLY-MESAM seven-channel ambulatory recording unit. Chest 2000 Jun;117(6):1613-8.

112. Fietze I, Glos M, Rottig J, Witt C. Automated analysis of data is inferior to visual analysis of ambulatory sleep apnea monitoring. Respiration 2002;69(3):235-41.

113. White DP, Gibb TJ, Wall JM, Westbrook PR. Assessment of accuracy and analysis time of a novel device to monitor sleep and breathing in the home. Sleep 1995 Feb;18(2):115-26.

114. Shochat T, Hadas N, Kerkhofs M, Herchuelz A, Penzel T, Peter JH, Lavie P. The SleepStrip: an apnoea screener for the early detection of sleep apnoea syndrome. Eur Respir J 2002 Jan;19(1):121-6.

115. Alvarez D, Hornero R, Abasolo D, del Campo F, Zamarron C. Nonlinear characteristics of blood oxygen saturation from nocturnal oximetry for obstructive sleep apnoea detection. Physiol Meas 2006 Apr;27(4):399-412.

116. Michaelson PG, Allan P, Chaney J, Mair EA. Validations of a portable home sleep study with twelve-lead polysomnography: comparisons and insights into a variable gold standard. Ann Otol Rhinol Laryngol 2006;115(11):802-9.

117. Pang KP, Dillard TA, Blanchard AR, Gourin CG, Podolsky R, Terris DJ. A comparison of polysomnography and the SleepStrip in the diagnosis of OSA. Otolaryngol Head Neck Surg 2006 Aug;135(2):265-8.

118. Yin M, Miyazaki S, Ishikawa K. Evaluation of type 3 portable monitoring in unattended home setting for suspected sleep apnea: factors that may affect its accuracy. Otolaryngol Head Neck Surg 2006 Feb;134(2):204-9.

119. Gurubhagavatula I, Maislin G, Nkwuo JE, Pack AI. Occupational screening for obstructive sleep apnea in commercial drivers. Am J Respir Crit Care Med 2004 Aug 15;170(4):371-6.

120. Pittman SD, Ayas NT, MacDonald MM, Malhotra A, Fogel RB, White DP. Using a wrist-worn device based on peripheral arterial tonometry to diagnose obstructive sleep apnea: In-laboratory and ambulatory validation. Sleep 2004 Aug 1;27(5):923-33.

121. Quintana-Gallego E, Villa-Gil M, Carmona-Bernal C, Botebol-Benhamou G, Martinez-Martinez A, Sanchez-Armengol A, Polo-Padillo J, Capote F. Home respiratory polygraphy for diagnosis of sleep-disordered breathing in heart failure. Eur Respir J 2004;24(3):443-8.

122. Su S, Baroody FM, Kohrman M, Suskind D. A comparison of polysomnography and a portable home sleep study in the diagnosis of obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2004 Dec;131(6):844-50.

123. Adachi H, Mikami A, Kumano-go T, Suganuma N, Matsumoto H, Shigedo Y, Sugita Y, Takeda M. Clinical significance of pulse rate rise during sleep as a screening marker for the assessment of sleep fragmentation in sleep-disordered breathing. Sleep Med 2003 Nov;4(6):537-42.

124. Zamarron C, Gude F, Barcala J, Rodriguez JR, Romero PV. Utility of oxygen saturation and heart rate spectral analysis obtained from pulse oximetric recordings in the diagnosis of sleep apnea syndrome. Chest 2003 May;123(5):1567-76.

125. Calleja JM, Esnaola S, Rubio R, Duran J. Comparison of a cardiorespiratory device versus polysomnography for diagnosis of sleep apnoea. Eur Respir J 2002 Dec 1;20(6):1505-10.

126. Golpe R, Jimenez A, Carpizo R. Home sleep studies in the assessment of sleep apnea/hypopnea syndrome. Chest 2002 Oct;122(4):1156-61.

127. Marrone O, Salvaggio A, Insalaco G, Bonsignore MR, Bonsignore G. Evaluation of the POLYMESAM system in the diagnosis of obstructive sleep apnea syndrome. Monaldi Arch Chest Dis 2001;56(6):486-90.

128. Baltzan MA, Verschelden P, Al-Jahdali H, Olha AE, Kimoff RJ. Accuracy of oximetry with thermistor (OxiFlow) for diagnosis of obstructive sleep apnea and hypopnea. Sleep 2000 Feb 1;23(1):61-9.

129. Vazquez JC, Tsai WH, Flemons WW, Masuda A, Brant R, Hajduk E, Whitelaw WA, Remmers JE. Automated analysis of digital oximetry in the diagnosis of obstructive sleep apnoea. Thorax 2000 Apr;55(4):302-7.

130. Chiner E, Signes-Costa J, Arriero JM, Marco J, Fuentes I, Sergado A. Nocturnal oximetry for the diagnosis of the sleep apnoea hypopnoea syndrome: a method to reduce the number of polysomnographies. Thorax 1999 Nov;54(11):968-71.

131. Mykytyn IJ, Sajkov D, Neill AM, McEvoy RD. Portable computerized polysomnography in attended and unattended settings. Chest 1999;115(1):114-22.

132. Zamarron C, Romero PV, Rodriguez JR, Gude F. Oximetry spectral analysis in the diagnosis of obstructive sleep apnoea. Clin Sci (Lond) 1999 Oct;97(4):467-73.

133. Mayer P, Meurice JC, Philip-Joet F, Cornette A, Rakotonanahary D, Meslier N, Pepin JL, Levy P, Veale D. Simultaneous laboratory-based comparison of ResMed Autoset with polysomnography in the diagnosis of sleep apnoea/hypopnoea syndrome. Eur Respir J 1998 Oct;12(4):770-5.

134. Gugger M. Comparison of ResMed AutoSet (version 3.03) with polysomnography in the diagnosis of the sleep apnoea/hypopnoea syndrome. Eur Respir J 1997 Mar;10(3):587-91.

135. Carrasco O, Montserrat JM, Lloberes P, Ascasco C, Ballester E, Fornas C, Rodriguez-Roisin R. Visual and different automatic scoring profiles of respiratory variables in the diagnosis of sleep apnoea-hypopnoea syndrome. Eur Respir J 1996 Jan;9(1):125-30.

136. Esnaola S, Duran J, Infante-Rivard C, Rubio R, Fernandez A. Diagnostic accuracy of a portable recording device (MESAM IV) in suspected obstructive sleep apnoea. Eur Respir J 1996;9(12):2597-605.

137. Fleury B, Rakotonanahary D, Hausser-Hauw C, Lebeau B, Guilleminault C. A laboratory validation study of the diagnostic mode of the Autoset system for sleep-related respiratory disorders. Sleep 1996;19(6):502-5.

138. Levy P, Pepin JL, Deschaux-Blanc C, Paramelle B, Brambilla C. Accuracy of oximetry for detection of respiratory disturbances in sleep apnea syndrome. Chest 1996 Feb;109(2):395-9.

139. Lloberes P, Montserrat JM, Ascaso A, Parra O, Granados A, Alonso P, Vilaseca I, Rodriguez-Roisin R. Comparison of partially attended night time respiratory recordings and full polysomnography in patients with suspected sleep apnoea/hypopnoea syndrome. Thorax 1996 Oct;51(10):1043-7.

140. Zucconi M, Ferini-Strambi L, Castronovo V, Oldani A, Smirne S. An unattended device for sleep-related breathing disorders: validation study in suspected obstructive sleep apnoea syndrome. Eur Respir J 1996 Jun;9(6):1251-6.

141. Bradley PA, Mortimore IL, Douglas NJ. Comparison of polysomnography with ResCare Autoset in the diagnosis of the sleep apnoea/hypopnoea syndrome. Thorax 1995 Nov;50(11):1201-3.

142. Gugger M, Mathis J, Bassetti C. Accuracy of an intelligent CPAP machine with in-built diagnostic abilities in detecting apnoeas: a comparison with polysomnography. Thorax 1995 Nov;50(11):1199-201.

143. Ryan PJ, Hilton MF, Boldy DA, Evans A, Bradbury S, Sapiano S, Prowse K, Cayton RM. Validation of British Thoracic Society guidelines for the diagnosis of the sleep apnoea/hypopnoea syndrome: can polysomnography be avoided. Thorax 1995 Sep;50(9):972-5.

144. Koziej M, Cieslicki JK, Gorzelak K, Sliwinski P, Zielinski J. Hand-scoring of MESAM 4 recordings is more accurate than automatic analysis in screening for obstructive sleep apnoea. Eur Respir J 1994 Oct;7(10):1771-5.

145. Issa FG, Morrison D, Hadjuk E, Iyer A, Feroah T, Remmers JE. Digital monitoring of sleep-disordered breathing using snoring sound and arterial oxygen saturation. Am Rev Respir Dis 1993 Oct;148(4 Pt 1):1023-9.

146. Rauscher H, Popp W, Zwick H. Model for investigating snorers with suspected sleep apnoea. Thorax 1993 Mar;48(3):275-9.

147. Series F, Marc I, Cormier Y, La Forge J. Utility of nocturnal home oximetry for case finding in patients with suspected sleep apnea hypopnea syndrome. Ann Intern Med 1993 Sep 15;119(6):449-53.

148. Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet 1992 Feb 8;339(8789):347-50.

149. Stoohs R, Guilleminault C. MESAM 4: an ambulatory device for the detection of patients at risk for obstructive sleep apnea syndrome (OSAS). Chest 1992 May;101(5):1221-7.

150. Emsellem HA, Corson WA, Rappaport BA, Hackett S, Smith LG, Hausfeld JN. Verification of sleep apnea using a portable sleep apnea screening device. South Med J 1990 Jul;83(7):748-52.

151. George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. Thorax 2001 Jul;56(7):508-12.

152. Scharf MB, Stover R, McDannold MD, Spinner O, Berkowitz DV, Conrad C. Outcome evaluation of long-term nasal continuous positive airway pressure therapy in obstructive sleep apnea. Am J Ther 1999;6(6):293-7.

153. Krieger J, Meslier N, Lebrun T, Levy P, Phillip-Joet F, Sailly JC, Racineux J. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: a prospective study. Chest 1997;112(6):1561-6.

154. Mazza S, Pepin JL, Naegele B, Rauch E, Deschaux C, Ficheux P, Levy P. Driving ability in sleep apnoea patients before and after CPAP treatment evaluation on a road safety platform. Eur Respir J 2006 Nov 1;28(5):1020-8. Epub 2006 Jul 26.

155. Hoekema A, Stegenga B, Bakker M, Brouwer WH, de Bont LG, Wijkstra PJ, van der Hoeven JH. Simulated driving in obstructive sleep apnoea-hypopnoea; effects of oral appliances and continuous positive airway pressure. Sleep Breath 2007 Sep;11(3):129-38.

156. George CF, Boudreau AC, Smiley A. Effects of nasal CPAP on simulated driving performance in patients with obstructive sleep apnoea. Thorax 1997 Jul;52(7):648-53.

157. Findley LJ, Fabrizio MJ, Knight H, Norcross BB, LaForte AJ, Suratt PM. Driving simulator performance in patients with sleep apnea. Am Rev Respir Dis 1989 Aug;140(2):529-30.

158. Orth M, Duchna HW, Leidag M, Widdig W, Rasche K, Bauer TT, Walther JW, de Zeeuw J, Malin JP, Schultze-Werninghaus G, Kotterba S. Driving simulator and neuropsychological [corrected] testing in OSAS before and under CPAP therapy. Eur Respir J 2005 Nov;26(5):898-903.

159. Turkington PM, Sircar M, Saralaya D, Elliott MW. Time course of changes in driving simulator performance with and without treatment in patients with sleep apnoea hypopnoea syndrome. Thorax 2004 Jan;59(1):56-9.

160. Buttner A, Ruhle KH. The therapeutic effect of theophylline on sustained attention in patients with obstructive sleep apnea. Somnologie 2003;7(1):23-7.

161. Hack MA, Choi SJ, Vijayapalan P, Davies RJ, Stradling JR. Comparison of the effects of sleep deprivation, alcohol and obstructive sleep apnoea (OSA) on simulated steering performance. Respir Med 2001 Jul;95(7):594-601.

162. Hack M, Davies RJ, Mullins R, Choi SJ, Ramdassingh-Dow S, Jenkinson C, Stradling JR. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. Thorax 2000 Mar;55(3):224-31.

163. Haraldsson PO, Carenfelt C, Lysdahl M, Tornros J. Long-term effect of uvulopalatopharyngoplasty on driving performance. Arch Otolaryngol Head Neck Surg 1995 Jan;121(1):90-4.

164. Ballester E, Badia JR, Hernandez L, Carrasco E, de Pablo J, Fornas C, Rodriguez-Roisin R, Montserrat JM. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999 Feb;159(2):495-501.

165. Bardwell WA, Ancoli-Israel S, Berry CC, Dimsdale JE. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: a placebo-controlled study. Psychosom Med 2001;63(4):579-84.

166. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, Pierce RJ. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004 Sep 15;170(6):656-64.

167. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003 Jan 7;107(1):68-73.

168. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J, Merino-Sanchez M, Gonzalez-Benitez MA, Beltran-Robles M, Almeida-Gonzalez C. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. Chest 2006 Jun;129(6):1459-67.

169. Carley DW, Olopade C, Ruigt GS, Radulovacki M. Efficacy of mirtazapine in obstructive sleep apnea syndrome. Sleep 2007 Jan 1;30(1):35-41.

170. Chakravorty I, Cayton RM, Szczepura A. Health utilities in evaluating intervention in the sleep apnoea/hypopnoea syndrome. Eur Respir J 2002 Nov 1;20(5):1233-8.

171. Coughlin SR, Mawdsley L, Mugarza JA, Wilding JP, Calverley PM. Cardiovascular and metabolic effects of CPAP in obese males with OSA. Eur Respir J 2007 Apr;29(4):720-7.

172. Engleman HM, Gough K, Martin SE, Kingshott RN, Padfield PL, Douglas NJ. Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea/hypopnea syndrome: effects in "non- dippers". Sleep - Europe 1996 Jun;19(5):378-81.

173. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. Lancet 1994 Mar 5;343(8897):572-5.

174. Ferguson KA, Heighway K, Ruby RRF. A randomized trial of laser-assisted uvulopalatoplasty in the treatment of mild obstructive sleep apnea. Am J Respir Crit Care Med 2003 Jan 1;167(1):15-19.

175. Haraldsson PO, Carenfelt C, Lysdahl M, Tingvall C. Does uvulopalatopharyngoplasty inhibit automobile accidents. Laryngoscope 1995 Jun;105(6):657-61.

176. Hein H, Behnke G, Jorres RA, Magnussen H. The therapeutic effect of theophylline in mild obstructive sleep Apnea/Hypopnea syndrome: results of repeated measurements with portable recording devices at home. Eur J Med Res 2000;5(9):391-9.

177. Henke KG, Grady JJ, Kuna ST. Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypopnea syndrome. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 2001 Mar;163(4):911-7.

178. Hirshkowitz M, Black JE, Wesnes K, Niebler G, Arora S, Roth T. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. Respir Med 2006 Aug 11;101(3):616-27. Epub 2006 Aug 14.

179. Hui DS, To KW, Ko FW, Fok JP, Chan MC, Ngai JC, Tung AH, Ho CW, Tong MW, Szeto CC, Yu CM. Nasal CPAP reduces systemic blood pressure in patients with obstructive sleep apnoea and mild sleepiness. Thorax 2006 Dec;61(12):1083-90.

180. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999 Jun 19;353(9170):2100-5.

181. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003 Mar 27;348(13):1233-41.

182. Lojander J, Maasilta P, Partinen M, Brander PE, Salmi T, Lehtonen H. Nasal-CPAP, surgery, and conservative management for treatment of obstructive sleep apnea syndrome: a randomized study. Chest 1996;110(1):114-119.

183. Lojander J, Kajaste S, Maasilta P, Partinen M. Cognitive function and treatment of obstructive sleep apnea syndrome. J Sleep Res 1999 Mar;8(1):71-6.

184. Loredo JS, Ancoli-Israel S, Kim EJ, Lim WJ, Dimsdale JE. Effect of continuous positive airway pressure versus supplemental oxygen on sleep quality in obstructive sleep apnea: a placebo-CPAP-controlled study. Sleep 2006 Apr 1;29(4):564-71.

185. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med 2004 Feb 1;169(3):361-6.

186. McArdle N, Douglas NJ. Effect of continuous positive airway pressure on sleep architecture in the sleep apnea-hypopnea syndrome: a randomized controlled trial. Am J Respir Crit Care Med 2001 Oct 15;164(8I):1459-63.

187. Monasterio C, Vidal S, Duran J, Ferrer M, Carmona C, Barbe F, Mayos M, Gonzalez-Mangado N, Juncadella M, Navarro A, Barreira R, Capote F, Mayoralas LR, Peces-Barba G, Alonso J, Montserrat JM. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;164(6):939-43.

188. Montserrat JM, Ferrer M, Hernandez L, Farre R, Vilagut G, Navajas D, Badia JR, Carrasco E, De Pablo J, Ballester E. Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. Am J Respir Crit Care Med 2001;164(4):608-13.

189. Norman D, Loredo JS, Nelesen RA, Ancoli-Israel S, Mills PJ, Ziegler MG, Dimsdale JE. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. Hypertension 2006 May;47(5):840-5.

190. Oberndorfer S, Saletu B, Gruber G, Anderer P, Saletu M, Mandl M, Saletu-Zyhlarz G. Theophylline in snoring and sleep-related breathing disorders: sleep laboratory investigations on subjective and objective sleep and awakening quality. Methods Find Exp Clin Pharmacol 2000 May;22(4):237-45.

191. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000 Dec 20;284(23):3015-21.

192. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. Eur Respir J 2006 Jun;27(6):1229-35.

193. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002 Jan 19;359(9302):204-10.

194. Rasche K, Duchna HW, Lauer J, Orth M, Kotterba S, Bauer TT, Gillissen A, Schultze-Werninghaus G. Obstructive Sleep Apnea and Hypopnea Efficacy and Safety of a Long-Acting beta2-Agonist. Sleep Breath 1999;3(4):125-130.

195. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax 2005;60(9):781-5.

196. Sampol G, Munoz X, Sagales MT, Marti S, Roca A, Dolors de la Calzada M, Lloberes P, Morell F. Long-term efficacy of dietary weight loss in sleep apnoea/hypopnoea syndrome. Eur Respir J 1998 Nov;12(5):1156-9.

197. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, Smith PL. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis 1991 Sep;144(3 Pt 1):494-8.

198. Usui K, Bradley TD, Spaak J, Ryan CM, Kubo T, Kaneko Y, Floras JS. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. J Am Coll Cardiol 2005 Jun 21;45(12):2008-11.

199. Woodson BT, Steward DL, Weaver EM, Javaheri S. A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2003;128(6):848-61.

200. Commonly used tests to assess sleep disorders. [internet]. Frazer (PA) : Cephalon, Inc.; 2003 Dec 9 [accessed 2007 Jun 8]. [2 p]. Available: http://www.cephalon.com/newsroom/assets/Commonly_Used_Sleep_Tests.pdf.

201. Orth MM, Grootoonk S, Duchna HW, de Zeeuw J, Walther JW, Bauer TT, Schultze-Werninghaus G, Rasche K. Short-term effects of oral theophylline in addition to CPAP in mild to moderate OSAS. Respir Med 2005;99(4):471-6.

202. Bao X, Nelesen RA, Loredo JS, Dimsdale JE, Ziegler MG. Blood pressure variability in obstructive sleep apnea: role of sympathetic nervous activity and effect of continuous positive airway pressure. Blood Press Monit 2002 Dec;7(6):301-7.

203. Wiest GH, Harsch IA, Fuchs FS, Kitzbichler S, Bogner K, Brueckl WM, Hahn EG, Ficker JH. Initiation of CPAP therapy for OSA: does prophylactic humidification during CPAP pressure titration improve initial patient acceptance and comfort? Respiration 2002;69(5):406-12.

204. Randerath WJ, Galetke W, David M, Siebrecht H, Sanner B, Ruhle K-H. Prospective randomized comparison of impedance-controlled auto-continuous positive airway pressure (APAPFOT) with constant CPAP. Sleep Med 2001;2(2):115-24.

205. Ficker JH, Fuchs FS, Wiest GH, Asshoff G, Schmelzer AH, Hahn EG. An auto-continuous positive airway pressure device controlled exclusively by the forced oscillation technique. Eur Respir J 2000 Nov;16(5):914-20.

206. Teschler H, Wessendorf TE, Farhat AA, Konietzko N, Berthon-Jones M. Two months auto-adjusting versus conventional nCPAP for obstructive sleep apnoea syndrome. Eur Respir J 2000 Jun;15(6):990-5.

207. Sharma S, Wali S, Pouliot Z, Peters M, Neufeld H, Kryger M. Treatment of obstructive sleep apnea with a self-titrating continuous positive airway pressure (CPAP) system. Sleep - Europe 1996 Jul;19(6):497-501.

208. Valencia-Flores M, Bliwise DL, Guilleminault C, Cilveti R, Clerk A. Cognitive function in patients with sleep apnea after acute nocturnal nasal continuous positive airway pressure (CPAP) treatment: sleepiness and hypoxemia effects. J Clin Exp Neuropsychol 1996 Apr;18(2):197-210.

209. Randerath WJ, Heise M, Hinz R, Ruehle KH. An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. Chest 2002 Aug;122(2):569-75.

210. Saletu B, Oberndorfer S, Anderer P, Gruber G, Divos H, Lachner A, Mandl M, Parapatics S, Popp W, Saletu M, Saletu-Zyhlarz G, Sertl K, Strobl R, Tschida U, Winkler A. Efficiency of continuous positive airway pressure versus theophylline therapy in sleep apnea: comparative sleep laboratory studies on objective and subjective sleep and awakening quality. Neuropsychobiology 1999;39(3):151-9.

211. Ferber C, Duclaux R, Mouret J. Naltrexone improves blood gas patterns in obstructive sleep apnoea syndrome through its influence on sleep. J Sleep Res 1993;2(3):149-55.

212. Cook WR, Benich JJ, Wooten SA. Indices of severity of obstructive sleep apnea syndrome do not change during medroxyprogesterone acetate therapy. Chest 1989 Aug;96(2):262-6.

213. Espinoza H, Antic R, Thornton AT, McEvoy RD. The effects of aminophylline on sleep and sleep-disordered breathing in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1987 Jul;136(1):80-4.

214. Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. Am J Respir Crit Care Med 2001 May;163(6):1457-61.

215. Brander PE, Soirinsuo M, Lohela P. Nasopharyngeal symptoms in patients with obstructive sleep apnea syndrome - effect of nasal cpap treatment. Respiration 1999 Mar-Apr;66(2):128-35.

216. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 2001;163(2):344-8.

217. Lindberg E, Berne C, Elmasry A, Hedner J, Janson C. CPAP treatment of a population based sample. What are the benefits and the treatment compliance? Sleep Med 2006;7(7):553-60.

218. Nussbaumer Y, Bloch KE, Genser T, Thurnheer R. Equivalence of autoadjusted and constant continuous positive airway pressure in home treatment of sleep apnea. Chest 2006;129(3):638-43.

219. Popescu G, Latham M, Allgar V, Elliott MW. Continuous positive airway pressure for sleep apnoea/hypopnoea syndrome: Usefulness of a 2 week trial to identify factors associated with long term use. Thorax 2001;56(9):727-33.

220. Rauscher H, Formanek D, Popp W, Zwick H. Self-reported vs measured compliance with nasal CPAP for obstructive sleep apnea. Chest 1993 Jun;103(6):1675-80.

221. Rauscher H, Popp W, Wanke T, Zwick H. Acceptance of CPAP therapy for sleep apnea. Chest 1991 Oct;100(4):1019-23.

222. Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. Am J Respir Crit Care Med 1994 Jan;149(1):149-54.

223. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. Chest 2006 Dec;130(6):1772-8.

224. Roth T, White D, Schmidt-Nowara W, Wesnes KA, Niebler G, Arora S, Black J. Effects of armodafinil in the treatment of residual excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome: a 12-week, multicenter, double-blind, randomized, placebo-controlled study in nCPAP-adherent adults. Clin Ther 2006 May;28(5):689-706.

225. Ball EM, Banks MB. Determinants of compliance with nasal continuous positive airway pressure treatment applied in a community setting. Sleep Med 2001 May;2(3):195-205.

226. Waldhorn RE, Herrick TW, Nguyen MC, O'Donnell AE, Sodero J, Potolicchio SJ. Long-term compliance with nasal continuous positive airway pressure therapy of obstructive sleep apnea. Chest 1990 Jan;97(1):33-8.

227. Sampol G, Rodes G, Romero O, Jurado MJ, Lloberes P. Adherence to nCPAP in patients with coronary disease and sleep apnea without sleepiness. Respir Med 2007 Mar;101(3):461-466.

228. Edinger JD, Carwile S, Miller P, Hope V, Mayti C. Psychological status, syndromatic measures, and compliance with nasal CPAP therapy for sleep apnea. Percept Mot Skills 1994 Jun;78(3 Pt 2):1116-8.

229. Pelletier-Fleury N, Rakotonanahary D, Fleury B. The age and other factors in the evaluation of compliance with nasal continuous positive airway pressure for obstructive sleep apnea syndrome. A Cox's proportional hazard analysis. Sleep Med 2001 May;2(3):225-232.

230. Weaver TE, Kribbs NB, Pack AI, Kline LR, Chugh DK, Maislin G, Smith PL, Schwartz AR, Schubert NM, Gillen KA, Dinges DF. Night-to-night variability in CPAP use over the first three months of treatment. Sleep 1997 Apr;20(4):278-83.

231. Bachour A, Maasilta P. Mouth breathing compromises adherence to nasal continuous positive airway pressure therapy. Chest 2004;126(4):1248-54.

232. Haniffa M, Lasserson TJ, Smith I. Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. In: Cochrane Database of Systematic Reviews [database online]. Issue 4. Hoboken (NJ): John Wiley & Sons, Ltd.; 2004 [accessed 2007 Mar 28]. [Art. No.: CD003531]. Available: DOI: 10.1002/14651858.CD003531.pub2.

233. Ayas NT, Patel SR, Malhotra A, Schulzer M, Malhotra M, Jung D, Fleetham J, White DP. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. Sleep 2004;27(2):249-53.

234. Chai CL, Pathinathan A, Smith B. Continuous positive airway pressure delivery intrfaces for obstructive sleep apnoea. In: Cochrane Database of Systematic Reviews [database online]. Issue 4. Hoboken (NJ): John Wiley & Sons, Ltd.; 2006 [accessed 2007 Mar 27]. [Art. No.:CD005308]. Available: DOI:10.1002/14651858.pub2.

235. Hussain SF, Love L, Burt H, Fleetham JA. A randomized trial of auto-titrating CPAP and fixed CPAP in the treatment of obstructive sleep apnea-hypopnea. Respir Med 2004 Apr;98(4):330-3.

236. Hukins C. Comparative study of autotitrating and fixed-pressure CPAP in the home: a randomized, single-blind crossover trial. Sleep 2004 Dec 15;27(8):1512-7.

237. Marrone O, Resta O, Salvaggio A, Giliberti T, Stefano A, Insalaco G. Preference for fixed or automatic CPAP in patients with obstructive sleep apnea syndrome. Sleep Med 2004 May;5(3):247-51.

238. Nolan GM, Doherty LS, Mc Nicholas WT. Autoadjusting versus fixed positive pressure therapy in mild to moderate obstructive sleep apnoea. Sleep 2007 Feb 1;30(2):189-94.

239. Galetke W, Anduleit N, Richter K, Stieglitz S, Randerath WJ. Comparison of automatic and continuous positive airway pressure in a night-by-night analysis: a randomized, crossover study. Respiration 2006 Dec 4;:Epub ahead of print.

240. Nilius G, Happel A, Domanski U, Ruhle KH. Pressure-relief continuous positive airway pressure vs constant continuous positive airway pressure: a comparison of efficacy and compliance. Chest 2006 Oct;130(4):1018-24.

241. Aloia MS, Stanchina M, Arnedt JT, Malhotra A, Millman RP. Treatment adherence and outcomes in flexible vs standard continuous positive airway pressure therapy. Chest 2005 Jun;127(6):2085-93.

242. Mador MJ, Krauza M, Pervez A, Pierce D, Braun M. Effect of heated humidification on compliance and quality of life in patients with sleep apnea using nasal continuous positive airway pressure. Chest 2005;128(4):2151-8.

243. Meurice JC, Ingrand P, Portier F, Arnulf I, Rakotonanahari D, Fournier E, Philip-Joet F, Veale D, The ANTADIR Working Group "PPC", CMTS ANTADIR. A multicentre trial of education strategies at CPAP induction in the treatment of severe sleep apnoea-hypopnoea syndrome. Sleep Med 2007 Jan;8(1):37-42.

244. Wiese HJ, Boethel C, Phillips B, Wilson JF, Peters J, Viggiano T. CPAP compliance: Video education may help!. Sleep Med 2005;6(2):171-4.

245. Lewis KE, Bartle IE, Watkins AJ, Seale L, Ebden P. Simple interventions improve re-attendance when treating the sleep apnoea syndrome. Sleep Med 2006 Apr;7(3):241-7.

246. Smith CE, Dauz ER, Clements F, Puno FN, Cook D, Doolittle G, Leeds W. Telehealth services to improve nonadherence: a placebo-controlled study. Telemed J E Health 2006 Jun;12(3):289-96.

247. DeMolles DA, Sparrow D, Gottlieb DJ, Friedman R. A pilot trial of a telecommunications system in sleep apnea management. Med Care 2004 Aug;42(8):764-9.

248. Taylor Y, Eliasson A, Andrada T, Kristo D, Howard R. The role of telemedicine in CPAP compliance for patients with obstructive sleep apnea syndrome. Sleep Breath 2006 Sep;10(3):132-8.

249. Nolan GM, Ryan S, O'connor TM, McNicholas WT. Comparison of three auto-adjusting positive pressure devices in patients with sleep apnoea. Eur Respir J 2006 Jul;28(1):159-64.

250. Moher D, Pham, Klassen TP, Schulz KF, Berlin JA, Jadad AR, Liberati A. What contributions do languages other than english make on the results of meta-analyses? J Clin Epidemiol 2000 Sep;53(9):964-72.

251. Juni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol 2002 Feb;31(1):115-23.

252. Desai AV, Marks GB, Jankelson D, Grunstein RR. Do sleep deprivation and time of day interact with mild obstructive sleep apnea to worsen performance and neurobehavioral function? J Clin Sleep Med 2006 Jan 15;2(1):63-70.

253. Pichel F, Zamarron C, Magan F, Rodriguez JR. Sustained attention measurements in obstructive sleep apnea and risk of traffic accidents. Respir Med 2006 Jun;100(6):1020-7.

254. Goncalves MA, Paiva T, Ramos E, Guilleminault C. Obstructive sleep apnea syndrome, sleepiness, and quality of life. Chest 2004 Jun;125(6):2091-6.

255. Sforza E, Haba-Rubio J, De Bilbao F, Rochat T, Ibanez V. Performance vigilance task and sleepiness in patients with sleep-disordered breathing. Eur Respir J 2004 Aug;24(2):279-85.

256. Desai AV, Ellis E, Wheatley JR, Grunstein RR. Fatal distraction: a case series of fatal fall-asleep road accidents and their medicolegal outcomes. Med J Aust 2003 Apr 21;178(8):396-9.

257. Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, Cappa SF. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 2003 Jun 30;61(1):87-92.

258. Powell NB, Schechtman KB, Riley RW, Li K, Guilleminault C. Sleepy driving: accidents and injury. Otolaryngol Head Neck Surg 2002 Mar;126(3):217-27.

259. Yee B, Campbell A, Beasley R, Neill A. Sleep disorders: a potential role in New Zealand motor vehicle accidents. Intern Med J 2002 Jul;32(7):297-304.

260. Fulda S, Schulz H. Cognitive dysfunction in sleep disorders. Sleep Med Rev 2001 Dec;5(6):423-445.

261. Juniper M, Hack MA, George CF, Davies RJ, Stradling JR. Steering simulation performance in patients with obstructive sleep apnoea and matched control subjects. Eur Respir J 2000 Mar;15(3):590-5.

262. Masa JF, Rubio M, Findley LJ. Habitually sleepy drivers have a high frequency of automobile crashes associated with respiratory disorders during sleep. Am J Respir Crit Care Med 2000 Oct;162(4 Pt 1):1407-12.

263. Randerath WJ, Gerdesmeyer C, Siller K, Gil G, Sanner B, Ruhle KH. A test for the determination of sustained attention in patients with obstructive sleep apnea syndrome. Respiration 2000;67(5):526-32.

264. Risser MR, Ware JC, Freeman FG. Driving simulation with EEG monitoring in normal and obstructive sleep apnea patients. Sleep 2000 May 1;23(3):393-8.

265. Findley LJ, Suratt PM, Dinges DF. Time-on-task decrements in 'steer clear' performance of patients with sleep apnea and narcolepsy. Sleep 1999 Sep 15;22(6):804-9.

266. Hakkanen H, Summala H, Partinen M, Tiihonen M, Silvo J. Blink duration as an indicator of driver sleepiness in professional bus drivers. Sleep 1999 Sep 15;22(6):798-802.

267. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J, Arroyo I, Garcia JI, Quintana I, Carpizo R, Cifrian J, Garcia MM, Golpe R. The association between sleep apnea and the risk of traffic accidents. N Engl J Med 1999 Mar 18;340(11):847-51.

268. George CF, Boudreau AC, Smiley A. Comparison of simulated driving performance in narcolepsy and sleep apnea patients. Sleep 1996 Nov;19(9):711-7.

269. George CF, Boudreau AC, Smiley A. Simulated driving performance in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1996 Jul;154(1):175-81.

270. Findley L, Unverzagt M, Guchu R, Fabrizio M, Buckner J, Suratt P. Vigilance and automobile accidents in patients with sleep apnea or narcolepsy. Chest 1995 Sep;108(3):619-24.

271. Horne JA, Reyner LA. Sleep related vehicle accidents. BMJ 1995 Mar 4;310(6979):565-7.

272. Naegele B, Thouvard V, Pepin JL, Levy P, Bonnet C, Perret JE, Pellat J, Feuerstein C. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep - Europe 1995 Jan;18(1):43-52.

273. Stoohs R. Sleeping at the wheel... an assessment of commercial truck drivers. RT 1995 Oct-Nov;8(6):35-6.

274. Bedard MA, Montplaisir J, Malo J, Richer F, Rouleau I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 1993 Mar;15(2):330-41.

275. Flemons WW, Remmers JE, Whitelaw WA. The correlation of a computer simulated driving program with polysomnographic indices and neuropsychological tests in consecutively referred patients for assessment of sleep apnea. Sleep - Europe 1993 Dec;16(8 Suppl):S71.

276. Minemura H, Akashiba T, Yamamoto H, Suzuki R, Itoh D, Kurashima K, Yoshizawa T, Horie T. Traffic accidents in obstructive sleep apnea patients and effect of nasal CPAP treatment. Jpn J Thorac Dis 1993;31(9):1103-8.

277. Telakivi T, Kajaste S, Partinen M, Brander P, Nyholm A. Cognitive function in obstructive sleep apnea. Sleep - Europe 1993 Dec;16(8 Suppl):S74-5.

278. Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 1992 Mar;152(3):538-41.

279. Bedard MA, Montplaisir J, Richer F, Malo J. Nocturnal hypoxemia as a determinant of vigilance impairment in sleep apnea syndrome. Chest 1991 Aug;100(2):367-70.

280. Scheltens P, Visscher F, Van Keimpema AR, Lindeboom J, Taphoorn MJ, Wolters EC. Sleep apnea syndrome presenting with cognitive impairment. Neurology 1991 Jan;41(1):155-6.

281. Haraldsson PO, Carenfelt C, Laurell H, Tornros J. Driving vigilance simulator test. Acta Otolaryngol 1990 Jul-Aug;110(1-2):136-40.

282. Findley LJ, Fabrizio M, Thommi G, Suratt PM. Severity of sleep apnea and automobile crashes. N Engl J Med 1989 Mar;320(13):868-9.

283. Gonzalez-Rothi RJ, Foresman GE, Block AJ. Do patients with sleep apnea die in their sleep? Chest 1988 Sep;94(3):531-8.

284. George CF, Nickerson PW, Hanly PJ. Sleep apnoea patients have more automobile accidents. Lancet 1987;2(8556):447.

285. Moller HJ, Kayumov L, Bulmash EL, Nhan J, Shapiro CM. Simulator performance, microsleep episodes, and subjective sleepiness: normative data using convergent methodologies to assess driver drowsiness. J Psychosom Res 2006 Sep;61(3):335-42.

286. Nabi H, Gueguen A, Chiron M, Lafont S, Zins M, Lagarde E. Awareness of driving while sleepy and road traffic accidents: prospective study in GAZEL cohort. BMJ 2006 Jul;333(7558).

287. Belz SM, Robinson GS, Casali JG. Temporal separation and self-rating of alertness as indicators of driver fatigue in commercial motor vehicle operators. Hum Factors 2004 Spring;46(1):154-69.

288. Lardelli-Claret P, Luna-Del-Castillo Jde D, Jimenez-Moleon JJ, Rueda-Dominguez T, Garcia-Martin M, Femia-Marzo P, Bueno-Cavanillas A. Association of main driver-dependent risk factors with the risk of causing a vehicle collision in Spain, 1990-1999. Ann Epidemiol 2003 Aug;13(7):509-17.

289. Randerath WJ, Schraeder O, Galetke W, Feldmeyer F, Ruhle KH. Autoadjusting CPAP therapy based on impedance efficacy, compliance and acceptance. Am J Respir Crit Care Med 2001 Mar;163(3 Pt 1):652-7.

290. Benbadis SR, Mascha E, Perry MC, Wolgamuth BR, Smolley LA, Dinner DS. Association between the Epworth sleepiness scale and the multiple sleep latency test in a clinical population. Ann Intern Med 1999 Feb 16;130(4 Pt 1):289-92.

291. Bennett LS, Barbour C, Langford B, Stradling JR, Davies RJ. Health status in obstructive sleep apnea: relationship with sleep fragmentation and daytine sleepiness, and effects of continuous positive airway pressure treatment. Am J Respir Crit Care Med 1999 Jun;159(6):1884-90.

292. Reyner LA, Horne JA. Falling asleep whilst driving: are drivers aware of prior sleepiness. Int J Legal Med 1998;111(3):120-3.

293. Bennett LS, Langford BA, Stradling JR, Davies RJ. Sleep fragmentation indices as predictors of daytime sleepiness and nCPAP response in obstructive sleep apnea. Am J Respir Crit Care Med 1998 Sep;158(3):778-86.

294. Olson LG, Cole MF, Ambrogetti A. Correlations among Epworth Sleepiness Scale scores, multiple sleep latency tests and psychological symptoms. J Sleep Res 1998 Dec;7(4):248-53.

295. Hers V, Liistro G, Dury M, Collard P, Aubert G, Rodenstein DO. Residual effect of nCPAP applied for part of the night in patients with obstructive sleep apnoea. Eur Respir J 1997;10(5):973-76.

296. Chervin RD, Aldrich MS, Pickett R, Guilleminault C. Comparison of the results of the Epworth Sleepiness Scale and the Multiple Sleep Latency Test. J Psychosom Res 1997 Feb;42(2):145-55.

297. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest 1993 Jan;103(1):30-6.

298. McEvoy RD, Thornton AT. Treatment of obstructive sleep apnea syndrome with nasal continuous positive airway pressure. Sleep 1984;7(4):313-25.

299. Ancoli-Israel S, Mason W, Coy TV, Stepnowsky C, Clausen JL, Dimsdale J. Evaluation of sleep disordered breathing with unattended recording: the Nightwatch System. J Med Eng Technol 1997 Jan-Feb;21(1):10-4.

300. Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT. Sleep 2005 Jan 1;28(1):123-44.

301. Ayappa I, Norman RG, Suryadevara M, Rapoport DM. Comparison of limited monitoring using a nasal-cannula flow signal to full polysomnography in sleep-disordered breathing. Sleep 2004 Sep 15;27(6):1171-9.

302. Ayas NT, Pittman S, MacDonald M, White DP. Assessment of a wrist-worn device in the detection of obstructive sleep apnea. Sleep Med 2003 Sep;4(5):435-42.

303. Bagnato MC, Nery LE, Moura SM, Bittencourt LR, Tufik S. Comparison of AutoSet and polysomnography for the detection of apnea-hypopnea events. Braz J Med Biol Res 2000 May;33(5):515-9.

304. Ballester E, Solans M, Vila X, Hernandez L, Quinto L, Bolivar I, Bardagi S, Montserrat JM. Evaluation of a portable respiratory recording device for detecting apnoeas and hypopnoeas in subjects from a general population. Eur Respir J 2000 Jul;16(1):123-7.

305. Bar A, Pillar G, Dvir I, Sheffy J, Schnall RP, Lavie P. Evaluation of a portable device based on peripheral arterial tone for unattended home sleep studies. Chest 2003 Mar;123(3):695-703.

306. Bonsignore G, Marrone O, Macaluso C, Salvaggio A, Stallone A, Bellia V. Validation of oximetry as a screening test for obstructive sleep apnoea syndrome. Eur Respir J Suppl 1990 Oct;11:542s-544s.

307. Cooper BG, Veale D, Griffiths CJ, Gibson GJ. Value of nocturnal oxygen saturation as a screening test for sleep apnoea. Thorax 1991 Aug;46(8):586-8.

308. Dingli K, Coleman EL, Vennelle M, Finch SP, Wraith PK, Mackay TW, Douglas NJ. Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome. Eur Respir J 2003 Feb;21(2):253-9.

309. Gagnadoux F, Pelletier-Fleury N, Philippe C, Rakotonanahary D, Fleury B. Home unattended vs hospital telemonitored polysomnography in suspected obstructive sleep apnea syndrome: a randomized crossover trial. Chest 2002 Mar;121(3):753-8.

310. Gyulay S, Gould D, Sawyer B, Pond D, Mant A, Saunders N. Evaluation of a microprocessor-based portable home monitoring system to measure breathing during sleep. Sleep - Europe 1987 Apr;10(2):130-42.

311. Harma M, Suvanto S, Popkin S, Pulli K, Mulder M, Hirvonen K. A dose-response study of total sleep time and the ability to maintain wakefulness. J Sleep Res 1998 Sep;7(3):167-74.

312. Iber C, Redline S, Kaplan Gilpin AM, Quan SF, Zhang L, Gottlieb DJ, Rapoport D, Resnick HE, Sanders M, Smith P. Polysomnography performed in the unattended home versus the attended laboratory setting--Sleep Heart Health Study methodology. Sleep 2004 May 1;27(3):536-40.

313. Man GC, Kang BV. Validation of a portable sleep apnea monitoring device. Chest 1995 Aug;108(2):388-93.

314. Orr WC, Eiken T, Pegram V, Jones R, Rundell OH. A laboratory validation study of a portable system for remote recording of sleep-related respiratory disorders. Chest 1994 Jan;105(1):160-2.

315. Osman EZ, Osborne J, Hill PD, Lee BW. The Epworth Sleepiness Scale: can it be used for sleep apnoea screening among snorers. Clin Otolaryngol Allied Sci 1999 Jun;24(3):239-41.

316. Overland B, Bruskeland G, Akre H, Skatvedt O. Evaluation of a portable recording device (Reggie) with actimeter and nasopharyngeal/esophagus catheter incorporated. Respiration 2005 Nov-Dec;72(6):600-5.

317. Penzel T, Kesper K, Pinnow I, Becker HF, Vogelmeier C. Peripheral arterial tonometry, oximetry and actigraphy for ambulatory recording of sleep apnea. Physiol Meas 2004 Aug;25(4):1025-36.

318. Pepin JL, Levy P, Lepaulle B, Brambilla C, Guilleminault C. Does oximetry contribute to the detection of apneic events? Mathematical processing of the SaO2 signal. Chest 1991 May;99(5):1151-7.

319. Pillar G, Bar A, Betito M, Schnall RP, Dvir I, Sheffy J, Lavie P. An automatic ambulatory device for detection of AASM defined arousals from sleep: the WP100. Sleep Med 2003 May;4(3):207-12.

320. Portier F, Portmann A, Czernichow P, Vascaut L, Devin E, Benhamou D, Cuvelier A, Muir JF. Evaluation of home versus laboratory polysomnography in the diagnosis of sleep apnea syndrome. Am J Respir Crit Care Med 2000 Sep;162(3 Pt 1):814-8.

321. Rauscher H, Popp W, Zwick H. Quantification of sleep disordered breathing by computerized analysis of oximetry, heart rate and snoring. Eur Respir J 1991 Jun;4(6):655-9.

322. Redline S, Tosteson T, Boucher MA, Millman RP. Measurement of sleep-related breathing disturbances in epidemiologic studies. Assessment of the validity and reproducibility of a portable monitoring device. Chest 1991 Nov;100(5):1281-6.

323. Rees K, Wraith PK, Berthon-Jones M, Douglas NJ. Detection of apnoeas, hypopnoeas and arousals by the AutoSet in the sleep apnoea/hypopnoea syndrome. Eur Respir J 1998 Oct;12(4):764-9.

324. Suzuki H, Moriguchi K, Matsuura M, Kojima T, Matsuda T, Noda Y, Minemura H, Yamamoto H, Akashiba T, Horie T. Two nap sleep test: an easy objective sleepiness test. Psychiatry Clin Neurosci 2000 Jun;54(3):285-6.

325. Van Surell C, Lemaigre D, Leroy M, Foucher A, Hagenmuller MP, Raffestin B. Evaluation of an ambulatory device, CID 102, in the diagnosis of obstructive sleep apnoea syndrome. Eur Respir J 1995 May;8(5):795-800.

326. Westbrook PR, Levendowski DJ, Cvetinovic M, Zavora T, Velimirovic V, Henninger D, Nicholson D. Description and validation of the apnea risk evaluation system: a novel method to diagnose sleep apnea-hypopnea in the home. Chest 2005 Oct;128(4):2166-75.

327. Whittle AT, Finch SP, Mortimore IL, MacKay TW, Douglas NJ. Use of home sleep studies for diagnosis of the sleep apnoea/hypopnoea syndrome. Thorax 1997 Dec;52(12):1068-73.

328. Williams AJ, Yu G, Santiago S, Stein M. Screening for sleep apnea using pulse oximetry and a clinical score. Chest 1991 Sep;100(3):631-5.

329. Yin M, Miyazaki S, Itasaka Y, Shibata Y, Abe T, Miyoshi A, Ishikawa K, Togawa K. A preliminary study on application of portable monitoring for diagnosis of obstructive sleep apnea. Auris Nasus Larynx 2005;32(2):151-6.

330. Findley LJ, Levinson MP, Bonnie RJ. Driving performance and automobile accidents in patients with sleep apnea. Clin Chest Med 1992 Sep;13(3):427-35.

331. Barry H. Does treating sleep apnea with nasal continuous positive airway pressure (CPAP) prevent car accidents? Evid Based Pract 2000 Jun;3(6):9-1.

332. Rauscher H, Formanek D, Popp W, Zwick H. Nasal CPAP and weight loss in hypertensive patients with obstructive sleep apnoea. Thorax 1993 May;48(5):529-33.

333. Loube DI, Loube AA, Erman MK. Continuous positive airway pressure treatment results in weight less in obese and overweight patients with obstructive sleep apnea. J Am Diet Assoc 1997 Aug;97(8):896-7.

334. Jokic R, Klimaszewski A, Crossley M, Sridhar G, Fitzpatrick MF. Positional treatment vs continuous positive airway pressure in patients with positional obstructive sleep apnea syndrome. Chest 1999 Mar;115(3):771-81.

335. Meurice JC, Marc I, Series F. Efficacy of auto-CPAP in the treatment of obstructive sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1996 Feb;153(2):794-8.

336. Teschler H, Berthon-Jones M, Thompson AB, Henkel A, Henry J, Konietzko N. Automated continuous positive airway pressure titration for obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996 Sep;154(3 Pt 1):734-40.

337. Feuerstein C, Naegele B, Pepin JL, Levy P. Frontal lobe-related cognitive functions in patients with sleep apnea syndrome before and after treatment. Acta Neurol Belg 1997 Jun;97(2):96-107.

338. Meurice JC, Paquereau J, Denjean A, Patte F, Series F. Influence of correction of flow limitation on continuous positive airway pressure efficiency in sleep apnoea/hypopnoea syndrome. Eur Respir J 1998 May;11(5):1121-7.

339. Ficker JH, Wiest GH, Lehnert G, Wiest B, Hahn EG. Evaluation of an auto-CPAP device for treatment of obstructive sleep apnoea. Thorax 1998 Aug;53(8):643-8.

340. Piccirillo JF, Gates GA, White DL, Schectman KB. Obstructive sleep apnea treatment outcomes pilot study. Otolaryngol Head Neck Surg 1998 Jun;118(6):833-44.

341. Hoy CJ, Vennelle M, Kingshott RN, Engleman HM, Douglas NJ. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? Am J Respir Crit Care Med 1999 APR;159(4):1096-100.

342. Stefanescu BM, Murphy WP, Hansell BJ, Fuloria M, Morgan TM, Aschner JL. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics 2003 Nov;112(5):1031-8.

343. Engleman HM, Cheshire KE, Deary IJ, Douglas NJ. Daytime sleepiness, cognitive performance and mood after continuous positive airway pressure for the sleep apnoea/hypopnoea syndrome. Thorax 1993 Sep;48(9):911-4.

344. Restrick LJ, Fox NC, Braid G, Ward EM, Paul EA, Wedzicha JA. Comparison of nasal pressure support ventilation with nasal intermittent positive pressure ventilation in patients with nocturnal hypoventilation. Eur Respir J 1993 Mar;6(3):364-70.

345. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993 Apr;147(4):887-95.

346. Montplaisir J, Bedard MA, Richer F, Rouleau I. Neurobehavioral manifestations in obstructive sleep apnea syndrome before and after treatment with continuous positive airway pressure. Sleep - Europe 1992 Dec;15(6 Suppl):S17-9.

347. Palmer S, Selvaraj S, Dunn C, Osman LM, Cairns J, Franklin D, Hulks G, Godden DJ. Annual review of patients with sleep apnea/hypopnea syndrome--a pragmatic randomised trial of nurse home visit versus consultant clinic review. Sleep Med 2004 Jan;5(1):61-5.

348. Kessler R, Weitzenblum E, Chaouat A, Iamandi C, Alliotte T. Evaluation of unattended automated titration to determine therapeutic continuous positive airway pressure in patients with obstructive sleep apnea. Chest 2003 Mar;123(3):704-10.

349. Douglas NJ, Engleman HM. Effects of CPAP on vigilance and related functions in patients with the sleep apnea/hypopnea syndrome. Sleep 2000 Jun 15;23 Suppl 4:S147-9.

350. Hui DS, Chan JK, Choy DK, Ko FW, Li TS, Leung RC, Lai CK. Effects of augmented continuous positive airway pressure education and support on compliance and outcome in a Chinese population. Chest 2000 May;117(5):1410-6.

351. Hoy CJ, Vennelle M, Kingshott RN, Engleman HM, Douglas NJ. Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999 Apr;159(4 Pt 1):1096-100.

352. Hoekema A. Efficacy and comorbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review and preliminary results of a randomized trial. Sleep Breath 2006 Jun;10(2):102-3.

353. Blanco J, Zamarron C, Abeleira Pazos MT, Lamela C, Suarez Quintanilla D. Prospective evaluation of an oral appliance in the treatment of obstructive sleep apnea syndrome. Sleep Breath 2005;9(1):20-5.

354. Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002 Sep 15;166(6):855-9.

355. Kingshott RN, Vennelle M, Hoy CJ, Engleman HM, Deary IJ, Douglas NJ. Predictors of improvements in daytime function outcomes with CPAP therapy. Am J Respir Crit Care Med 2000;161(3 I):866-71.

356. Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. J Sleep Res 1997;6(3):199-204.

357. Stammnitz A, Jerrentrup A, Penzel T, Peter JH, Vogelmeier C, Becker HF. Automatic CPAP titration with different self-setting devices in patients with obstructive sleep apnoea. Eur Respir J 2004;24(2):273-8.

358. Tan YK, L'Estrange PR, Luo YM, Smith C, Grant HR, Simonds AK, Spiro SG, Battagel JM. Mandibular advancement splints and continuous positive airway pressure in patients with obstructive sleep apnoea: a randomized cross-over trial. Eur J Orthod 2002;24(3):239-49.

359. Gotsopoulos H, Chen C, Qian J, Cistulli PA. Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166(5):743-8.

360. Munoz A, Mayoralas LR, Barbe F, Pericas J, Agusti AG. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. Eur Respir J 2000;15(4):676-81.

361. Sachez AI, Buela-Casal G, Paz Bermudez M, Cabello-Salas R. Effects of nCPAP treatment over reaction time and sleepiness levels during vigilance. Clin Neuropsychol 2004 May;18(2):277-83.

362. Puhan MA, Suarez A, Lo Cascio C, Zahn A, Heitz M, Braendli O. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. BMJ 2006 Feb 4;332(7536):266-70.

363. Marshall NS, Neill AM, Campbell AJ, Sheppard DS. Randomised controlled crossover trial of humidified continuous positive airway pressure in mild obstructive sleep apnoea. Thorax 2005 May;60(5):427-32.

364. Roizenblatt S, Guilleminault C, Poyares D, Cintra F, Kauati A, Tufik S. A double-blind, placebo-controlled, crossover study of sildenafil in obstructive sleep apnea. Arch Intern Med 2006 Sep 18;166(16):1763-7.

365. Bailey DR. Dental therapy for obstructive sleep apnea. Semin Respir Crit Care Med 2005 Feb;26(1):89-95.

366. Dort LC, Hussein J. Snoring and obstructive sleep apnea: compliance with oral appliance therapy. J Otolaryngol 2004 Jun;33(3):172-6.

367. Coughlin SR, Mugarza JA, Mawdsley L, Wilding JP, Calverley PM. Continuous positive airways pressure treatment reduces the cardiovascular risk factors associated with obstructive sleep apnoea [poster: 111]. In: American Thoracic Society 100th international conference; 2004 May 21-26; Orlando. American Thoracic Society; 2004. C99.

368. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Peter JH. Effect of therapeutic and subtherapeutic nasal continuous positive airway pressure (nCPAP) treatment on blood pressure in obstructive sleep apnea (OSA). Sleep Med 2003;4(Suppl 1):S3.

369. Egea C, Pinto J, Ayuela J, Ballester E, Zamarron C, Sojo A, et al. Efficacy of the treatment with CPAP in patients with chronic heart failure and sleep apnoea. Eur Respir J 2004;24(Suppl 48):564S.

370. Lam B, Sam K, Cheung MT, Mok W, Lam J, Tsang KW, et al. A randomized controlled study for the treatment of mild/moderate obstructive sleep apnea (OSA) [abstract]. Sleep Med 2003;4(Suppl 1):S26.

371. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. J Clin Endocrinol Metab 2004 Sep;89(9):4409-13.

372. Berry RB, Kouchi K, Bower J, Prosise G, Light RW. Triazolam in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1995 Feb;151(2 Pt 1):450-4.

373. Issa FG. Effect of clonidine in obstructive sleep apnea. Am Rev Respir Dis 1992 Feb;145(2 Pt 1):435-9.

374. Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest 1991 Aug;100(2):416-21.

375. Stepanski EJ, Conway WA, Young DK, Zorick FJ, Wittig RM, Roth T. A double-blind trial of protriptyline in the treatment of sleep apnea syndrome. Henry Ford Hosp Med J 1988;36(1):5-8.

376. Suratt PM, Wilhoit SC, Brown ED, Findley LJ. Effect of doxapram on obstructive sleep apnea. Bull Eur Physiopathol Respir 1986 Mar-Apr;22(2):127-31.

377. Rubin AH, Alroy GG, Peled R, Lavie P. Preliminary clinical experience with imipramine HCl in the treatment of sleep apnea syndrome. Eur Neurol 1986;25(2):81-5.

378. Guilleminault C, Hayes B. Naloxone, theophylline, bromocriptine, and obstructive sleep apnea. Negative results. Bull Eur Physiopathol Respir 1983 Nov-Dec;19(6):632-4.

379. Brownell LG, Perez-Padilla R, West P, Kryger MH. The role of protriptyline in obstructive sleep apnea. Bull Eur Physiopathol Respir 1983 Nov-Dec;19(6):621-4.

380. Kumar R. Drug profile. Modafinil helps promote wakefulness. Evid Based Pract 2004 Dec;7(12):9-10.

381. Boyd B, Castaner J. Armodafinil. treatment of excessive sleepiness a1- adrenoceptor agonist. Drugs Future 2006;31(1):17-21.

382. Schwartz JR. Modafinil: new indications for wake promotion. Expert Opin Pharmacother 2005;6(1):115-29.

383. Walsh JT, Andrews R, Starling R, Cowley AJ, Johnston IDA, Kinnear WJ. Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure. Br Heart J 1995;73(3):237-41.

384. Cross MD, Vennelle M, Engleman HM, White S, Mackay TW, Twaddle S, Douglas NJ. Comparison of CPAP titration at home or the sleep laboratory in the sleep apnea hypopnea syndrome. Sleep 2006 Nov 1;29(11):1451-5.

385. West SD, Jones DR, Stradling JR. Comparison of three ways to determine and deliver pressure during nasal CPAP therapy for obstructive sleep apnoea. Thorax 2006 Mar;61(3):226-31.

386. Duong M, Jayaram L, Camfferman D, Catcheside P, Mykytyn I, McEvoy RD. Use of heated humidification during nasal CPAP titration in obstructive sleep apnoea syndrome. Eur Respir J 2005 Oct;26(4):679-85.

387. Resta O, Carratu P, Depalo A, Giliberti T, Ardito M, Marrone O, Insalaco G. Effects of fixed compared to automatic CPAP on sleep in Obstructive Sleep Apnoea Syndrome. Monaldi Arch Chest Dis 2004 Jul-Sep;61(3):153-6.

388. Noseda A, Kempenaers C, Kerkhofs M, Braun S, Linkowski P, Jann E. Constant vs auto-continuous positive airway pressure in patients with sleep apnea hypopnea syndrome and a high variability in pressure requirement. Chest 2004 Jul;126(1):31-7.

389. Randerath WJ, Galetke W, Ruhle KH. Auto-adjusting CPAP based on impedance versus bilevel pressure in difficult-to-treat sleep apnea syndrome: a prospective randomized crossover study. Med Sci Monit 2003 Aug;9(8):CR353-8.

390. Juhasz J, Becker H, Cassel W, Rostig S, Peter JH. Proportional positive airway pressure: a new concept to treat obstructive sleep apnoea. Eur Respir J 2001 Mar;17(3):467-73.

391. Hudgel DW, Fung C. A long-term randomized, cross-over comparison of auto-titrating and standard nasal continuous airway pressure. Sleep 2000 Aug 1;23(5):645-8.

392. Pepin JL, Krieger J, Rodenstein D, Cornette A, Sforza E, Delguste P, Deschaux C, Grillier V, Levy P. Effective compliance during the first 3 months of continuous positive airway pressure. A European prospective study of 121 patients. Am J Respir Crit Care Med 1999 Oct;160(4):1124-9.

393. Massie CA, Hart RW, Peralez K, Richards GN. Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. Chest 1999;116(2):403-8.

394. Konermann M, Sanner BM, Vyleta M, Laschewski F, Groetz J, Sturm A, Zidek W. Use of conventional and self-adjusting nasal continuous positive airway pressure for treatment of severe obstructive sleep apnea syndrome: a comparative study. Chest 1998 Mar;113(3):714-8.

395. Kushida CA, Nichols DA, Quan SF, Goodwin JL, White DP, Gottlieb DJ, Walsh JK, Schweitzer PK, Guilleminault C, Simon RD, Leary EB, Hyde PR, Holmes TH, Bloch DA, Green S, McEvoy LK, Gevins A, Dement WC. The Apnea Positive Pressure Long-term Efficacy Study (APPLES): Rationale, design, methods, and procedures. J Clin Sleep Med 2006 Jul 15;2(3):288-300.

396. Malik NW, Kenyon GS. Changes in the nasal airway mucosa and in nasal symptoms following continuous positive airway pressure (N-CPAP) for obstructive sleep apnoea. Aust J Otolaryngol 2004;7(1):17-20.

397. Sanders MH. Articles reviewed: Does lack of daytime sleepiness relate to benefits of continuous positive airway pressure on the consequences of obstructive sleep apnea/hypopnea? Design considerations demonstrated by two recent articles. Sleep Med 2002;3(1):83-6.

398. Choi S, Mullins R, Crosby JH, Davies RJO, Stradling JR. Is (re)titration of nasal continuous positive airway pressure for obstructive sleep apnoea necessary? Sleep Med 2001;2(5):431-5.

399. Farre R, Hernandez L, Montserrat JM, Rotger M, Ballester E, Navajas D. Sham continuous positive airway pressure for placebo-controlled studies in sleep apnoea. Lancet 1999 Apr 03;353(9159):1154.

400. Hoster M, Schlenker E, Ruhle KH. Computerised nCPAP titration compared with conventional constant nCPAP. Pneumologie 51(Suppl 3):754-7. (Ger).

401. Ficker JH, Muller D, Wiest G, Lehnert G, Dertinger SH, Katalinic A, Hahn EG. Nasal continuous versus bilevel positive airway pressure for obstructive sleep apnea (OSA): a prospective randomized study of acceptance during the initiation of therapy. Pneumologie 1997;51(6):586-91. (Ger).

402. Dixon JB, Schachter LM, O'Brien PE. Polysomnography before and after weight loss in obese patients with severe sleep apnea. Int J Obes (Lond) 2005 Sep;29(9):1048-54.

403. Hong S, Dimsdale JE. Physical activity and perception of energy and fatigue in obstructive sleep apnea. Med Sci Sports Exerc 2003 Jul;35(7):1088-92.

404. Hsu PP, Tan AK, Tan BY, Gan EC, Chan YH, Blair RL, Lu PK. Uvulopalatopharyngoplasty outcome assessment with quantitative computer-assisted videoendoscopic airway analysis. Acta Otolaryngol 2007;127(1):65-70.

405. Lin SW, Chen NH, Li HY, Fang TJ, Huang CC, Tsai YH, Lee CH. A comparison of the long-term outcome and effects of surgery or continuous positive airway pressure on patients with obstructive sleep apnea syndrome. Laryngoscope 2006;116(6):1012-6.

406. De Luca S. Review: Surgery is not effective for obstructive sleep apnoea hypopnoea syndrome in adults. Evid Based Med 2006;11(4):106.

407. Kezirian EJ, Goldberg AN. Hypopharyngeal surgery in obstructive sleep apnea: An evidence-based medicine review. Arch Otolaryngol Head Neck Surg 2006;132(2):206-213.

408. Rodrigues Thuler E, Silveira Dibern R, Fomin DS, De Oliveira JA. Laser-assisted uvulopalatoplasty - comparative analisys of the clinical improvement and the indication criteria. Rev Bras Otorinolaringol 2002;68(2):190-3.

409. Hattori C, Nishimura T, Kawakatsu K, Hayakawa M, Suzuki K. Comparison of surgery and nasal continuous positive airway pressure treatment for obstructive sleep apnea syndrome. Acta Otolaryngol Suppl 2003;550:46-50.

410. Finkelstein Y, Shapiro-Feinberg M, Stein G, Ophir D. Uvulopalatopharyngoplasty vs laser-assisted uvulopalatoplasty: anatomical considerations. Arch Otolaryngol Head Neck Surg 1997;123(3):265-276.

411. Bardwell WA, Norman D, Ancoli-Israel S, Loredo JS, Lowery A, Lim W, Dimsdale JE. Effects of 2-week nocturnal oxygen supplementation and continuous positive airway pressure treatment on psychological symptoms in patients with obstructive sleep apnea: a randomized placebo-controlled study. Behav Sleep Med 2007;5(1):21-38.

412. Freire AO, Sugai GC, Chrispin FS, Togeiro SM, Yamamura Y, Mello LE, Tufik S. Treatment of moderate obstructive sleep apnea syndrome with acupuncture: a randomised, placebo-controlled pilot trial. Sleep Med 2007 Jan;8(1):43-50.

413. Suratt PM, McTier RF, Findley LJ, Pohl SL, Wilhoit SC. Effect of very-low-calorie diets with weight loss on obstructive sleep apnea. Am J Clin Nutr 1992 Jul;56(1 Suppl):182S-184S.

414. Pasquali R, Colella P, Cirignotta F, Mondini S, Gerardi R, Buratti P, Rinaldi Ceroni A, Tartari F, Schiavina M, Melchionda N, et al. Treatment of obese patients with obstructive sleep apnea syndrome (OSAS): effect of weight loss and interference of otorhinolaryngoiatric pathology. Int J Obes (Lond) 1990 Mar;14(3):207-17.

415. Rubinstein I, Colapinto N, Rotstein LE, Brown IG, Hoffstein V. Improvement in upper airway function after weight loss in patients with obstructive sleep apnea. Am Rev Respir Dis 1988 Nov;138(5):1192-5.

416. Suratt PM, McTier RF, Findley LJ, Pohl SL, Wilhoit SC. Changes in breathing and the pharynx after weight loss in obstructive sleep apnea. Chest 1987 Oct;92(4):631-7.

417. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. Ann Intern Med 1985 Dec;103(6 (Pt 1)):850-5.

418. Harman EM, Wynne JW, Block AJ. The effect of weight loss on sleep-disordered breathing and oxygen desaturation in morbidly obese men. Chest 1982 Sep;82(3):291-4.

419. Stradling J, Roberts D, Wilson A, Lovelock F. Controlled trial of hypnotherapy for weight loss in patients with obstructive sleep apnoea. Int J Obes (Lond) 1998;22(3):278-81.

420. Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. Sleep Med 2003 Sep;4(5):393-402.

421. Kajaste S, Brander PE, Telakivi T, Partinen M, Mustajoki P. A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study. Sleep Med 2004 Mar;5(2):125-31.

422. Haraldsson PO, Carenfelt C, Persson HE, Sachs C, Tornros J. Simulated long-term driving performance before and after uvulopalatopharyngoplasty. ORL J Otorhinolaryngol Relat Spec 1991;53(2):106-10.

423. Findley LJ. Automobile driving in sleep apnea. Prog Clin Biol Res 1990;345:337-43; discussion 344-5.

424. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. Cochrane Database Syst Rev 2006;(1):CD001106.

425. Walker-Engstrom M, Tegelberg A, Wilhelmsson B, Ringqvist I. 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: a randomized study. Chest 2002 Mar;121(3):739-46.

426. Steward DL, Weaver EM, Woodson BT. Multilevel temperature-controlled radiofrequency for obstructive sleep apnea: extended follow-up. Otolaryngol Head Neck Surg 2005;132(4):630-5.

427. Steward DL, Weaver EM, Woodson BT. A comparison of radiofrequency treatment schemes for obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2004;130(5):579-85.

428. Arnulf I, Homeyer P, Garma L, Whitelaw WA, Derenne JP. Modafinil in obstructive sleep apnea-hypopnea syndrome: a pilot study in 6 patients. Respiration 1997;64(2):159-61.

429. Allison C. Obstructive sleep apnea: a palatable treatment option? Issues Emerg Health Technol 2007 Jan;(97):1-4.

430. Walker RP, Levine HL, Hopp ML, Greene D, Pang K. Palatal implants: a new approach for the treatment of obstructive sleep apnea. Otolaryngol Head Neck Surg 2006 Oct;135(4):549-54.

431. Nordgard S, Stene BK, Skjostad KW. Soft palate implants for the treatment of mild to moderate obstructive sleep apnea. Otolaryngol Head Neck Surg 2006 Apr;134(4):565-70.

432. Friedman M, Vidyasagar R, Bliznikas D, Joseph NJ. Patient selection and efficacy of pillar implant technique for treatment of snoring and obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg 2006 Feb;134(2):187-96.

433. McMahon JP, Foresman BH, Chisholm RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. Wis Med J 2003;102(1):36-43.

434. Hoekema A, Stegenga B, DeBont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. Crit Rev Oral Biol Med 2004;15(3):137-55.

435. Hedner J, Grunstein R, Eriksson B, Ejnell H. A double-blind, randomized trial of sabeluzole - a putative glutamate antagonistin - in obstructive sleep apnea. Sleep 1996;19(4):287-9.

436. Smith I, Lasserson TJ, Wright J. Drug therapy for obstructive sleep apnoea in adults. In: Cochrane Database of Systematic Reviews [database online]. Issue 2. Hoboken (NJ): John Wiley & Sons, Ltd.; 2006 [accessed 2007 Mar 28]. [Art. No.: CD003002]. Available: DOI:10.1002/14651858.CD003002.pub2.

437. Shneerson J, Wright J. Lifestyle modification for obstructive sleep apnoea. In: Cochrane Database of Systematic Reviews [database online]. Issue 1. Hoboken (NJ): John Wiley & Sons, Ltd.; 2007 [accessed 2007 Mar 28]. [Art. No.: CD002875]. Available: DOI:10.1002/14651858.CD002875.

438. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea (Review). In: Cochrane Database of Systematic Reviews [database online]. Issue 1. Hoboken (NJ): John Wiley & Sons, Ltd.; 2006 [accessed 2007 Mar 6]. [Art. No.: CD004435]. Available: DOI: 10.1002/14651858.CD004435.pub3.

439. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med 2005 Nov 14;165(20):2408-13.

440. Lequeux T, Chantrain G, Bonnand M, Chelle AJ, Thill MP. Physiotherapy in obstructive sleep apnea syndrome: preliminary results. Eur Arch Otorhinolaryngol 2005 Jun;262(6):501-3.

441. Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. Sleep 2004 May 1;27(3):480-4.

442. Lojander J, Mustajoki P, Ronka S, Mecklin P, Maasilta P. A nurse-managed weight reduction programme for obstructive sleep apnoea syndrome. J Intern Med 1998 Sep;244(3):251-5.

443. Kansanen M, Vanninen E, Tuunainen A, Pesonen P, Tuononen V, Hartikainen J, Mussalo H, Uusitupa M. The effect of a very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome. Clin Physiol 1998 Jul;18(4):377-85.

444. Kaleth AS, Chittenden TW, Hawkins BJ, Hargens TA, Guill SG, Zedalis D, Gregg JM, Herbert WG. Unique cardiopulmonary exercise test responses in overweight middle-aged adults with obstructive sleep apnea. Sleep Med 2007;8(2):160-8.

445. Friedman M, Vidyasagar R, Bliznikas D, Joseph N. Does severity of obstructive sleep apnea/hypopnea syndrome predict uvulopalatopharyngoplasty outcome? Laryngoscope 2005;115(12):2109-13.

446. Cincik H, Cekin E, Cetin B, Gungor A, Poyrazoglu E. Comparison of uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty and cautery-assisted uvulopalatoplasty in the treatment of primary snoring. ORL J Otorhinolaryngol Relat Spec 2006;68(3):149-155.

447. Han D, Ye J, Lin Z, Wang J, Wang J, Zhang Y. Revised uvulopalatopharyngoplasty with uvula preservation and its clinical study. ORL J Otorhinolaryngol Relat Spec 2005;67(4):213-219.

448. Jiang GF, Sun W, Li N, Sun Y, Zhang NK. Treatment effect of uvulopalatopharyngoplasty on autonomic nervous activity during sleep in patients with obstructive sleep apnea syndrome. Chin Med J (Engl) 2004;117(5):761-3.

449. Isono S, Shimada A, Tanaka A, Ishikawa T, Nishino T, Konno A. Effects of uvulopalatopharyngoplasty on collapsibility of the retropalatal airway in patients with obstructive sleep apnea. Laryngoscope 2003 Feb 1;113(2):362-7.

450. Lysdahl M, Haraldsson PO. Uvulopalatopharyngoplasty versus laser uvulopalatoplasty: prospective long-term follow-up of self-reported symptoms. Acta Otolaryngol 2002;122(7):752-7.

451. Finkelstein Y, Stein G, Ophir D, Berger R, Berger G. Laser-assisted uvulopalatoplasty for the management of obstructive sleep apnea myths and facts. Arch Otolaryngol Head Neck Surg 2002;128(4):429-34.

452. Boudewyns AN, De Backer WA, Van de Heyning PH. Pattern of upper airway obstruction during sleep before and after uvulopalatopharyngoplasty in patients with obstructive sleep apnea. Sleep Med 2001;2(4):309-15.

453. Millman RP, Carlisle CC, Rosenberg C, Kahn D, McRae R, Kramer NR. Simple predictors of uvulopalatopharyngoplasty outcome in the treatment of obstructive sleep apnea. Chest 2000;118(4):1025-1030.

454. Ryan CF, Love LL. Unpredictable results of laser assisted uvulopalatoplasty in the treatment of obstructive sleep apnoea. Thorax 2000;55(5):399-404.

455. Bridgman SA, Dunn KM. Systematic review of the surgical treatment of obstructive sleep apnoea. J Clin Excel 2000;1(4):217-20.

456. Walker RP, Garrity T, Gopalsami C. Early polysomnographic findings and longterm subjective results in sleep apnea patients treated with laser-assisted uvulopalatoplasty. Laryngoscope 1999;109(9):1438-41.

457. Remacle M, Betsch C, Lawson G, Jamart J, Eloy P. A new technique for laser-assisted uvulopalatoplasty: decision-tree analysis and results. Laryngoscope 1999;109(5):763-8.

458. Mickelson SA, Ahuja A. Short-term objective and long-term subjective results of laser-assisted uvulopalatoplasty for obstructive sleep apnea. Laryngoscope 1999;109(3):362-7.

459. Isberg A, Levring-Jaghagen E, Dahlstrom M, Dahlqvist A. Persistent dysphagia after laser uvulopalatoplasty: a videoradiographic study of pharyngeal function. Acta Otolaryngol 1998;118(6):870-4.

460. Woodson BT, Conley SF, Dohse A, Feroah TR, Sewall SR, Fujita S. Posterior cephalometric radiographic analysis in obstructive sleep apnea. Ann Otol Rhinol Laryngol 1997;106(4):310-313.

461. Janson C, Gislason T, Bengtsson H, Eriksson G, Lindberg E, Lindholm CE, Hultcrantz E, Hetta J, Boman G. Long-term follow-up of patients with obstructive sleep apnea treated with uvulopalatopharyngoplasty. Arch Otolaryngol Head Neck Surg 1997;123(3):257-62.

462. Cahali MB, Formigoni GG, Gebrim EM, Miziara ID. Lateral pharyngoplasty versus uvulopalatopharyngoplasty: a clinical, polysomnographic and computed tomography measurement comparison. Sleep 2004 Aug 1;27(5):942-50.

463. Alajmi M, Mulgrew AT, Fox J, Davidson W, Schulzer M, Mak E, Ryan CF, Fleetham J, Choi P, Ayas NT. Impact of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea hypopnea: a meta-analysis of randomized controlled trials. Lung 2007 Mar-Apr;185(2):67-72. Epub 2007 Mar.

464. Phillips BA, Schmitt FA, Berry DT, Lamb DG, Amin M, Cook YR. Treatment of obstructive sleep apnea. A preliminary report comparing nasal CPAP to nasal oxygen in patients with mild OSA. Chest 1990 Aug;98(2):325-30.

465. Cirignotta F, Mondini S, Zucconi M, Gerardi R, Farolfi A, Lugaresi E. Zolpidem-polysomnographic study of the effect of a new hypnotic drug in sleep apnea syndrome. Pharmacol Biochem Behav 1988 Apr;29(4):807-9.

466. Reeves-Hoche MK, Hudgel DW, Meck R, Witteman R, Ross A, Zwillich CW. Continuous versus bilevel positive airway pressure for obstructive sleep apnea. Am J Respir Crit Care Med 1995 Feb;151(2 Pt 1):443-9.

467. Meston N, Davies RJ, Mullins R, Jenkinson C, Wass JA, Stradling JR. Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. J Intern Med 2003 Nov;254(5):447-54.

468. Oki Y, Shiomi T, Sasanabe R, Maekawa M, Hirota I, Usui K, Hasegawa R, Kobayashi T. Multiple cardiovascular risk factors in obstructive sleep apnea syndrome patients and an attempt at lifestyle modification using telemedicine-based education. Psychiatry Clin Neurosci 1999 Apr;53(2):311-3.

469. Weil JV, Cherniack NS, Dempsey JA, Edelman NH, Phillipson EA, Remmers JE, Kiley JP. NHLBI workshop summary. Respiratory disorders of sleep. Pathophysiology, clinical implications, and therapeutic approaches. Am Rev Respir Dis 1987 Sep;136(3):755-61.

470. Collop NA, Block AJ, Hellard D. The effect of nightly nasal CPAP treatment on underlying obstructive sleep apnea and pharyngeal size. Chest 1991 Apr;99(4):855-60.

471. Issa FG, Sullivan CE. The immediate effects of nasal continuous positive airway pressure treatment on sleep pattern in patients with obstructive sleep apnea syndrome. Electroencephalogr Clin Neurophysiol 1986 Jan;63(1):10-7.

472. Ryan CF, Lowe AA, Li D, Fleetham JA. Magnetic resonance imaging of the upper airway in obstructive sleep apnea before and after chronic nasal continuous positive airway pressure therapy. Am Rev Respir Dis 1991 Oct;144(4):939-44.

473. Strohl KP, Cherniack NS, Gothe B. Physiologic basis of therapy for sleep apnea. Am Rev Respir Dis 1986 Oct;134(4):791-802.

474. Kribbs NB, Gelsy JE, Dinges DF. Investigation and management of daytime sleepiness in sleep apnea. In: Saunders NA, Sullivan CE, editors. Sleep and breathing. New York: Marcel Dekker; 1993. p. 575-604.

475. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002 Feb 7;346(6):393-403.

476. Ellen RL, Marshall SC, Palayew M, Molnar FJ, Wilson KG, Man-Son-Hing M. Systematic review of motor vehicle crash risk in persons with sleep apnea. J Clin Sleep Med 2006 Apr 15;2(2):193-200.

477. Packham S, Ebden P. Recent advances in the sleep apnoea/hypopnoea syndrome. Hosp Med 2000 Feb;61(2):108-11.

478. Pichon Riviere A, Augustovski F, Alcaraz A, Bardach A, Ferrante D, Garcia Marte S, Lopez A, Glujovsky D, Regueiro A. Outpatient BiPAP (bi-level positive airway pressure) in obstructive sleep apnea. Ciudad de Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS); 2006.

479. Franklin K, Lundgren R, Dahlqvist A, Rabben T, Rosenhall L. [Nasal CPAP--treatment of choice in obstructive sleep apnea]. Nord Med 1992;107(2):42-5. (Swe).

480. Greenham-Conway BA. Compliance with continuous positive airway pressure therapy improves mood and psychological functioning in sleep-apnea-hypopnea syndrome. Diss Abstr Int B 2003;61(6B):3277.

481. Sin DD, Mayers I, Man GCW, Pawluk L. Longterm compliance rates to continuous positive airway pressure in obstructive sleep apnea a populationbased study. Chest 2002;121(2):430-35.

482. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath 2007 Mar;11(1):1-22.

483. Fletcher EC, Luckett RA. The effect of positive reinforcement on hourly compliance in nasal continuous positive airway pressure users with obstructive sleep apnea. Am Rev Respir Dis 1991 May;143(5 Pt 1):936-41.

484. Mortimore IL, Whittle AT, Douglas NJ. Comparison of nose and face mask CPAP therapy for sleep apnoea. Thorax 1998 Apr;53(4):290-2.

485. Means MK, Edinger JD, Husain AM. CPAP compliance in sleep apnea patients with and without laboratory CPAP titration. Sleep Breath 2004 Mar;8(1):7-14.

486. Aloia MS, Di Dio L, Ilniczky N, Perlis ML, Greenblatt DW, Giles DE. Improving compliance with nasal CPAP and vigilance in older adults with OAHS. Sleep Breath 2001;5(1):13-21.

487. Anttalainen U, Saaresranta T, Kalleinen N, Aittokallio J, Vahlberg T, Polo O. CPAP adherence and partial upper airway obstruction during sleep. Sleep Breath 2007 Sep;11(3):171-6.

488. Scharf SM, DeMore J, Landau T, Smale P. Comparison of primarycare practitioners and sleep specialists in the treatment of obstructive sleep apnea. Sleep Breath 2004;8(3):111-24.

489. Stepnowsky Jr CJ, Dimsdale JE. Doseresponse relationship between CPAP compliance and measures of sleep apnea severity. Sleep Med 2002;3(4):329-34.

490. Fitzpatrick MF, Alloway CE, Wakeford TM, MacLean AW, Munt PW, Day AG. Can patients with obstructive sleep apnea titrate their own continuous positive airway pressure. Am J Respir Crit Care Med 2003 Mar 1;167(5):716-22.

491. Chervin RD, Theut S, Bassetti C, Aldrich MS. Compliance with nasal CPAP can be improved by simple interventions. Sleep - Europe 1997;20:284-9.

492. Rauscher H, Popp W, Wanke T, Zwick H. Breathing during sleep in patients treated for obstructive sleep apnea. Nasal CPAP for only part of the night. Chest 1991 Jul;100(1):156-9.

493. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Arch Intern Med 2007 Mar 26;167(6):540-9.

494. Tjin SC, Tan YK, Yow M, Lam YZ, Hao J. Recording compliance of dental splint use in obstructive sleep apnoea patients by force and temperature modelling. Med Biol Eng Comput 2001 Mar;39(2):182-4.

495. Gagnadoux F, Rakotonanahary D, Martins de Araujo MT, Barros-Vieira S, Fleury B. Long-term efficacy of fixed CPAP recommended by Autoset for OSAS. Sleep 1999 Dec 15;22(8):1095-9.

496. Sanders MH, R Costantino J, Strollo PJ Jr, Studnicki K, Atwood CW Jr. The impact of splitnight polysomnography for diagnosis and positive pressure therapy titration on treatment acceptance and adherence in sleep apnea/hypopnea. Sleep 2000;23(1):1724.

497. Issa F, Grunstein R, Bruderer J, et al. Five years' experience with home nasal continuous positive airway pressure therapy for the obstructive sleep panea syndrome. In: Peter JH, Podszus T, von Wichert P, editors. Sleep related disorders and internal disease. Berlin: Springer-Verlag; 1987. p. 360-5.

498. Noseda A, Kempenaers C, Kerkhofs M, Houben JJ, Linkowski P. Sleep apnea after 1 year domiciliary nasal-continuous positive airway pressure and attempted weight reduction. Potential for weaning from continuous positive airway pressure. Chest 1996 Jan;109(1):138-43.

499. Issa E, Costas L, Berthan-Jones M, McCauley V, Brodorer J, Sullivan C. Nasal CPAP treatment for obstructive sleep apnea (OSA): long-term experience with 117 patients. Am Rev Respir Dis 1985;181:A108.

500. Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther 2005 Jul-Aug;22(4):313-56.

501. d'Ortho M, Grillier-Lanoir V, Levy P, Goldenberg F, Corriger E, Harf A, Lofaso F. Constant vs automatic continuous positive airway pressure therapy: home evaluation. Chest 2000 Oct;118(4):1010-7.

502. Collard P, Cornette P, Aubert G, Rodenstein DO. Sleep apnoea-hypopnoea syndrome: a polysomnographic study before and after proplonged continuous airway pressure therapy (abstract). Eur Respir J 1992;5:21S.

503. Campos-Rodriguez F, Pena-Grinan N, Reyes-Nunez N, De La Cruz-Moron I, Perez-Ronchel J, De La Vega-Gallardo F, Fernandez-Palacin A. Mortality in obstructive sleep apneahypopnea patients treated with positive airway pressure. Chest 2005;128(2):624-33.

504. Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. Thorax 1994 Mar;49(3):263-6.

505. Hui DSC, Ko FWS, Chan JKW, To KW, Fok JPC, Ngai JC, Chan MCH, Tung A, Chan DP, Ho CW, Lai CKW. Sleepdisordered breathing and continuous positive airway pressure compliance in a group of commercial bus drivers in Hong Kong. Respirology 2006;11(6):723-30.

506. Likar LL, Panciera TM, Erickson AD, Rounds S. Group education sessions and compliance with nasal CPAP therapy. Chest 1997 May;111(5):1273-7.

507. Krieger J. Long-term compliance with nasal continuous positive airway pressure (CPAP) in obstructive sleep apnea patients and nonapneic snorers. Sleep - Europe 1992 Dec;15(6 Suppl):S42-6.

508. Beecroft J, Zanon S, Lukic D, Hanly P. Oral continuous positive airway pressure for sleep apnea: effectiveness, patient preference, and adherence. Chest 2003 Dec;124(6):2200-8.

509. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest 2005 Jun;127(6):2076-84.

510. Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, Hirshkowitz M, Loube DL, Bailey D, Berry RB, Kapen S, Kramer M. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005 Jan 1;28(1):113-21.

511. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, Boehlecke B, Brown TM, Coleman J Jr, Friedman L, Kapen S, Kapur VK, Kramer M, Lee-Chiong T, Owens J, Pancer JP, Swick TJ, Wise MS, American Academy of Sleep Medicine. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep 2006 Mar 1;29(3):375-80.

512. Kushida CA, Morgenthaler TI, Littner MR, Alessi CA, Bailey D, Coleman J Jr, Friedman L, Hirshkowitz M, Kapen S, Kramer M, Lee-Chiong T, Owens J, Pancer JP. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. Sleep 2006 Feb 1;29(2):240-3.

513. Scottish Intercollegiate Guidelines Network (SIGN). Management of obstructive sleep apnoea/hypopnoea syndrome in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2003 Jun. 35 p. (SIGN publication; no. 73).

514. Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of obstructive sleep apnea. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Mar. 53 p.

515. Ferguson KA, Ono T, Lowe AA, Keenan SP, Fleetham JA. A randomized crossover study of an oral appliance vs nasal-continuous positive airway pressure in the treatment of mild-moderate obstructive sleep apnea. Chest 1996 May;109(5):1269-75.

516. Sullivan CE, Issa FG. Obstructive sleep apnea. Clin Chest Med 1985 Dec;6(4):633-50.

517. Bradshaw DA, Ruff GA, Murphy DP. An oral hypnotic medication does not improve continuous positive airway pressure compliance in men with obstructive sleep apnea. Chest 2006 Nov;130(5):1369-76.

518. Stepnowsky CJ Jr, Moore PJ. Nasal CPAP treatment for obstructive sleep apnea: developing a new perspective on dosing strategies and compliance. J Psychosom Res 2003;54(6):599-605.

519. Jokic R, Klimaszewski A, Sridhar G, Fitzpatrick MF. Continuous positive airway pressure requirement during the first month of treatment in patients with severe obstructive sleep apnea. Chest 1998 Oct;114(4):1061-9.

520. Massie CA, Hart RW. Clinical outcomes related to interface type in patients with obstructive sleep apnea/hypopnea syndrome who are using continuous positive airway pressure. Chest 2003 Apr;123(4):1112-8.

521. Meslier N, Lebrun T, Grillier-Lanoir V, Rolland N, Henderick C, Sailly JC, Racineux JL. A French survey of 3,225 patients treated with CPAP for obstructive sleep apnoea: benefits, tolerance, compliance and quality of life. Eur Respir J 1998 Jul;12(1):185-92.

522. Parthasarathy S, Haynes PL, Budhiraja R, Habib MP, Quan SF. A National Survey of the Effect of Sleep Medicine Specialists and American Academy of Sleep Medicine accreditation on management of obstructive sleep apnea. J Clin Sleep Med 2006 Apr 15;2(2):133-42.

523. Sullivan CE, Issa FG, Berthon-Jones M, McCauley VB, Costas LJ. Home treatment of obstructive sleep apnoea with continuous positive airway pressure applied through a nose-mask. Bull Eur Physiopathol Respir 1984 Jan-Feb;20(1):49-54.

524. Ross SD, Allen IE, Harrison KJ, Kvasz M, Connelly J, Sheinhait IA. Systematic review of the literature regarding the diagnosis of sleep apnea. Rockville (MD): Agency for Health Care Research and Policy; 1999. 154 p.

525. Roche N, Durieux P. Evaluation of the application of nocturnal nasal continuous positive airway pressure (CPAP) in the treatment of obstructive sleep apnea. Paris: Haute Autorite de sante/French National Authority for Health (HAS); 1992. 82 p.

526. Wiest GH, Foerst J, Fuchs FS, Schmelzer AH, Hahn EG, Ficker JH. In vivo efficacy of two heated humidifiers used during CPAP-therapy for obstructive sleep apnea under various environmental conditions. Sleep 2001 Jun 15;24(4):435-40.

527. Teschler H, Farhat AA, Exner V, Konietzko N, Berthon-Jones M. AutoSet nasal CPAP titration: constancy of pressure, compliance and effectiveness at 8 month follow-up. Eur Respir J 1997 Sep;10(9):2073-8.

528. Krieger J, Kurtz D, Petiau C, Sforza E, Trautmann D. Long-term compliance with CPAP therapy in obstructive sleep apnea patients and in snorers. Sleep - Europe 1996 Nov;19(9 Suppl):S136-43.

529. Sullivan CE, Issa FG, Berthon-Jones M, Saunders NA. Pathophysiology of sleep apnea. In: Saunders NA, Sullivan CE, editors. Sleep and breathing. New York: Marcel Dekker; 1984. p. 299-364.

530. Smith DM, Stradling JR. Can mandibular advancement devices be a satisfactory substitute for short term use in patients on nasal continuous positive airway pressure? Thorax 2002 Apr;57(4):305-8.

531. Sullivan CE, Berthon-Jones M, Issa FG. Remission of severe obesity-hypoventilation syndrome after short-term treatment during sleep with nasal continuous positive airway pressure. Am Rev Respir Dis 1983 Jul;128(1):177-81.

532. Tyrrell J, Poulet C, Pepin JL, Veale D. A preliminary study of psychological factors affecting patients' acceptance of CPAP therapy for sleep apnoea syndrome. Sleep Med 2006;7(4):375-79.

533. van Dulmen S, Sluijs E, van Dijk L, de Ridder D, Heerdink R, Bensing J. Patient adherence to medical treatment: a review of reviews. BMC Health Serv Res 2007 Apr 17;7(1):55.

534. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [internet]. Ottawa (ON): Ottawa Health Research Institute (OHRI); [accessed 2006 May 11]. [2 p]. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

Appendix A: Search Summaries

Search Summary for Key Questions 1 through 3

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), EMTREE, PsycINFO, and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific, related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = publication type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OLDMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = text word

Topic-specific Search Terms

Sleep Apnea

Apnea
Apne$
Apnoe$
OSA
Sleep apnea syndrome
Sleep apnea syndromes
Sleep disordered breathing
Sleepiness

Accidents

Accident$
Accidents, traffic
Collision$
Crash$
Highway safety
Motor traffic accidents
Traffic accident
Traffic safety
Wreck$

Driving

Auto$
Automobile driving
Automobiles
Car
exp Car driving
Commercial
Driving
exp Driving behavior
Haul$
Long distance
exp Motor vehicle
exp Motor vehicles
Professional
Truck

Mental Processes

Aware$
Choice behavior
Cognition
Continuous performance test
Divided attention task
Eye movement
Mental function
Mental processes
Neuropsychological performance
Perceptual motor processes
Performance
Psychomotor
Psychomotor performance
Reaction time
Response latency
Risk taking
Road tracking test
Unaware$

CINAHL/EMBASE/MEDLINE/PsycINFO

English language, human

Set Number	Concept	Search Statement	# Identified	# Downloaded
1	Sleep apnea	exp sleep apnea syndromes/ or sleep apnea syndrome.de. or apnea.de. or exp sleep disordered breathing/ or apne$ or apnoe$ or sleepiness	56239	
2	Limit by publication type	1 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)	40398	
3	Limit to English language, human population		30982	
4	Limit by population	3 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$ or neonat$ or infan$)	10209	
5		4 and adult	2488	
6		4 not 5	7721	
7		3 not 6	23261	
8	Driving	7 and (automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or (driving or commercial or professional or truck or car or auto$ or long distance or haul$).ti.) Remove duplicates	916 516	
9	Accidents	7 and ((accidents, traffic or highway safety or motor traffic accidents or traffic accident or traffic safety).de. or (crash$ or wreck$ or collision$ or accident$).ti.) Remove duplicates	369 252	
10	Cognition	7 and (Exp mental processes/ or exp psychomotor/ or exp neuropsychological performance or exp performance/ or exp reaction time/ or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/) Remove duplicates	5542 4831	
11	Attention	7 and (Aware or continuous performance test or road tracking test or divided attention task or eye movement or unaware) Remove duplicates	1389 839	
	Combine sets	or/8-11	6930	
19	Remove overlap		5354	816

Questions 1 - 3	Total Identified	Total Downloaded	Total in Database (unique citations)	Total Articles Received	Total Cited
	5354	**661**	**661**	**383 (436 requested)**	

Search Summary for Key Question 4

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

MeSH, EMTREE, PsycINFO, and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = publication type

[sb] = subset of PubMed database (PreMEDLINE, Systematic, OLDMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = text word

Topic-specific Search Terms

Sleep Apnea

Apnea

Apne$

Apnoe$

OSA

Sleep apnea syndrome

Sleep apnea syndromes

Sleep disordered breathing

Sleepiness

Diagnosis

accuracy

exp diagnosis

diagnosis.fs.

false negative

false positive

likelihood

precision

exp prediction and forecasting

predictive value of tests

receiver operating characteristic

ROC curve

Sensitivity

specificity

true negative

true positive

CINAHL/EMBASE/MEDLINE/PsycINFO

English language, human

Set Number	Concept	Search Statement	# Identified	# Downloaded
1	Sleep apnea	exp sleep apnea syndromes/ or sleep apnea syndrome.de. or apnea.de. or exp sleep disordered breathing/ or apne$ or apnoe$ or sleepiness	56239	
2	Limit by publication type	1 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)	40398	
3	Limit to English language, human population		30982	
4	Limit by population	3 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$ or neonat$ or infan$)	10209	
5		4 and adult	2488	
6		4 not 5	7721	
7		3 not 6	23261	
8	Screening	7 and (Screening or mass screening.de. or screen$.ti.) Remove duplicates	645 401	
9	Diagnosis	7 and (exp diagnosis/ or exp prediction and forecasting/ or di.fs. or (predictive value of tests or receiver operating characteristic or ROC curve or sensitivity and specificity or accuracy or diagnostic accuracy or precision or likelihood).de. or ((false or true) adj (positive or negative))) Remove duplicates	5555 4589	
10	Limit subset by study type	9 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study or evaluation studies or follow-up studies).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)	1443	
	Combine sets	8 or 10	1793	
	Remove overlap		1771	

Question	Tota Identified	Total Downloaded	Total in Database (unique citations)	Total Articles Received	Total Cited
	1771	430	430	379 (391 requested)	

Search Summary for Key Questions 5 and 6

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

MeSH, EMTREE, PsycINFO, and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp ="explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. =limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = publication type

[sb] = subset of PubMed database (PreMEDLINE, Systematic, OLDMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = text word

Topic-specific Search Terms

Sleep Apnea

Apnea
Apne$
Apnoe$
OSA
Sleep apnea syndrome
Sleep apnea syndromes
Sleep disordered breathing
Sleepiness

Drug Therapy

Ar-modafinil
Modafinil
Nuvigil
Provigil
Sleep apnea syndrome/drug therapy
Sleep apnea syndromes/drug therapy

CPAP

BiPap
CPAP
CPAP
Continuous positive airway pressure
Continuous positive pressure breathing
Positive end expiratory pressure
Positive-pressure breathing

Behavior Modification

Exp behavior modification
Behavior modification
Diet
Dieting
Exp exercise
Exercise$
Lifestyle
Life style
Exp lifestyle and related phenomena
Motor activity
Exp physical activity
Risk reduction behavior
Sports
Walking
Weight loss

Intraoral Appliances

Dental appliance$
Dental device$
Herbst
Intraoral appliance$
Intraoral device$
Intraoral mandibular repositioner
Mandibular advancement
Mandibular reposition$
Mandibular splint$
Maxillofacial prosthesis
Oral appliance$
Oral device$
Protruding appliance$
Protruding device$
Silencer
Twin block

Surgery

Exp oral surgical procedures
Exp oral surgery
Exp otorhinolaryngologic surgical procedures

CINAHL/EMBASE/MEDLINE/PsycINFO

English language, human

Set Number	Concept	Search Statement	# Identified	# Downloaded
1	Sleep apnea	exp sleep apnea syndromes/ or sleep apnea syndrome.de. or apnea.de. or exp sleep disordered breathing/ or apne$ or apnoe$ or sleepiness	56239	
2	Limit by publication type	1 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)	40398	
3	Limit to English language, human population		30982	
4	Limit by population	3 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$ or neonat$ or infan$)	10209	
5		4 and adult	2488	
6		4 not 5	7721	
7		3 not 6	23261	
8	Limit to Therapeutics	7 and ((th or su or dt).fs. or effectiveness or effectiveness or efficacy or intention to treat or treat or treatment or therapy or therapeutic or outcome assessment or relative risk or number needed to treat or NNT)	10949	
9	Limit by study type	7 and ((Randomized controlled trials or random allocation or double-blind method or single-blind method or placebos or cross-over studies or crossover procedure or double blind procedure or single blind procedure or placebo or latin square design or crossover design or double-blind studies or single-blind studies or triple-blind studies or random assignment or exp controlled study/ or exp clinical trial/ or exp comparative study/ or cohort analysis or follow-up studies.de. or intermethod comparison or parallel design or control group or prospective study or retrospective study or case control study or major clinical study).de. or random$.hw. or random$.ti. or placebo$ or ((singl$ or doubl$ or tripl$ or trebl$) and (dummy or blind or sham)) or latin square or ISRTCN)	8726	
10		7 and (Outcome$ or treatment outcome.de. or follow-up or longitudinal or long-term or cohort studies.de.)	4601	
11	Combine sets	or/8-10	15480	
12	Drug therapy	11 and (Modafinil or ar-modafinil or R-modafinil or nuvigl or provigil or *sleep apnea syndrome/dt or *sleep apnea syndromes/dt) Remove duplicates	465 334	
13	CPAP	11 and ((Positive end expiratory pressure or continuous positive airway pressure or positive-pressure breathing).de. or cpap or continuous positive airway pressure or continuous positive pressure breathing or bipap or CPAP) Remove duplicates	3096 1960	
14	Limit subset by study type	13 and (randomized controlled trial.pt. or randomized controlled trial.de. or random$.ti. or RCT.ti.)	220	
15	Behavior Modification	11 and (Exp behavior modification/ or exp exercise/ or exp physical activity/ or exp lifestyle and related phenomena/ or (behavior modification or lifestyle or life style or exerci?e$ or walking or dieting or weight loss).ti,ab. or (diet or risk reduction behavior or life style or exercise or sports or motor activity).de.) Remove duplicates	757 561	
16	Appliances	11 and ((Intraoral mandibular repositioner or mandibular advancement or maxillofacial prosthesis).de.or ((oral or intraoral or dental or protruding) adj (appliance$ or device$)) or Herbst or twin block or silencer or (mandib$ adj2 (splint$ or advance$ or reposition$.ti,ab.))) Remove duplicates	536 374	
17	Surgery	11 and (exp otorhinolaryngologic surgical procedures/ or exp oral surgery/ or exp oral surgical procedures/) Remove duplicates	995 865	

Set Number	Concept	Search Statement		# Identified	# Downloaded
18	Combine sets	or/12-17		2643	
19	Remove overlap			2052	816
Questions 5 & 6	**Total Identified**	**Total Downloaded**	**Total in Database (unique citations)**	**Total Articles Received**	**Total Cited**
	2052	**816**	**781**	**232**	

Search summary for Key Question 7

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

MeSH, EMTREE, PsycINFO, and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = publication type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OLDMEDLINE)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = text word

Topic-specific Search Terms

Sleep Apnea

Apnea

Apne$

Apnoe$

OSA

Sleep apnea syndrome

Sleep apnea syndromes

Sleep disordered breathing

Sleepiness

Compliance

Adher$

Complian$

Non-adher$

Nonadher$

Patient compliance.de.

CINAHL/EMBASE/MEDLINE/PsycINFO

English language, human

Set Number	Concept	Search Statement	# Identified	# Downloaded
1	Sleep apnea	exp sleep apnea syndromes/ or sleep apnea syndrome.de. or apnea.de. or exp sleep disordered breathing/ or apne$ or apnoe$ or sleepiness	56239	
2	Limit by publication type	1 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)	40398	
3	Limit to English language, human population		30982	
4	Limit by population	3 and (exp child/ or adolescent.de. or child$ or pediatr$ or paediatr$ or juvenile$ or adolescen$ or teen$ or youth$ or neonat$ or infan$)	10209	
5		4 and adult	2488	
6		4 not 5	7721	
7		3 not 6	23261	
8	Compliance	7 and (Patient compliance.de. or (complian$ or adher$ or non-adher$ or nonadher$).ti.) Remove duplicates	254 218	

Question 7	Total Identified	Total Downloaded	Total in Database (unique citations)	Total Articles Received	Total Cited
	218	**115**	**111**	**102 (106 requested)**	

Appendix B: Retrieval Criteria

Appendix B will list the retrieval criteria for each key question. An example of a small set of retrieval criteria are presented below.

Retrieval Criteria for Key Question 1

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for a fatal or nonfatal crash) associated with OSA.
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have OSA.

Retrieval Criteria for Key Question 2

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Studies that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.

Retrieval Criteria for Key Question 3

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Studies that did not address the relationship between subjective sleepiness and objective sleepiness in OSA individuals were excluded.

Retrieval Criteria for Key Question 4

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe sleep studies that were performed with both facility-based PSG and portable monitors in the same patients, either simultaneously or within three months of the first measurement.

Retrieval Criteria for Key Question 5

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.

Retrieval Criteria for Key Question 6

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the length of time required following initiation of an effective treatment for individuals with OSA to reach a degree of improvement that would permit safe driving (as determined through indirect measures of crash risk; i.e., driving simulators or cognitive/psychomotor functioning) or to show improvement in the risk factors associated with OSA (i.e., disease severity, daytime sleepiness, SaO_2, blood pressure).

Retrieval Criteria for Key Question 7

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Studies that did not address the relationship between treatment noncompliance and/or treatment withdrawal and time to recurrence of increased crash risk in individuals OSA were excluded.

Appendix C: Inclusion Criteria

Appendix C lists the inclusion criteria for each of the seven key questions addressed in this evidence report.

Inclusion Criteria for Key Question 1

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Studies were limited to individuals with OSA only,(no central apneas).
- Studies that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- Article must describe a study that attempted to directly determine the risk for a motor vehicle crash (risk for a fatal or nonfatal crash) associated with OSA using a direct measure of crash (no indirect measures; e.g., driving simulator data).
- Article must describe a study that includes a comparison group comprised of comparable subjects who do not have OSA.
- Article must present motor vehicle crash-risk data in a manner that will allow ECRI Institute to calculate (directly or through imputation) effect-size estimates and confidence intervals.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted to avoid double-counting individuals.

Inclusion Criteria for Key Question 2

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Studies were limited to individuals with OSA only (no central apneas).

- Studies that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- Article must describe a study that attempted to determine the disease-related factors associated with an increased risk for a motor vehicle crash (risk for a fatal or nonfatal crash) among individuals with OSA.
- Article must describe a study that includes a comparison group comprised of comparable subjects with OSA who did not have a motor vehicle crash.
- Article must present motor vehicle crash-risk data in a manner that will allow ECRI Institute to calculate (directly or through imputation) effect-size estimates and confidence intervals.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted to avoid double-counting individuals.

Inclusion Criteria for Key Question 3

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)
- Studies with a limited number of subjects - Case reports and trials with less than 10 subjects per arm were excluded.
- Studies were limited to individuals with OSA only (no central apneas).
- The relationship between subjective sleepiness and objective sleepiness was studied in OSA individuals. Studies that did not address the study question were excluded.
- Trials that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- Studies published prior to 1990 were excluded from analysis.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted to avoid double-counting individuals.

Inclusion Criteria for Key Question 4

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.

- Individuals with OSA only, no central apneas.
- Studies that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- Article must describe sleep studies that were performed with both facility-based PSG and portable monitors in the same patients , either simultaneously or within three months of the first measurement.
- Article must report outcome in terms of sensitivity and specificity of portable monitors relative to PSG AI, AHI, or present data in a manner that will allow ECRI Institute to calculate sensitivity and specificity of portable monitors.

Inclusion Criteria for Key Question 5

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Studies were limited to individuals with OSA only (no central apneas).
- Studies that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash (fatal or nonfatal crash) associated with OSA following treatment using direct measures (i.e., crash risk), quasi-direct measures (i.e., simulated driving performance), or indirect measures (i.e., OSA severity, EDS, cognitive and psychomotor function, blood pressure, SaO_2).
- Article must describe a study that includes a comparison group comprised of comparable individuals who do not have OSA or have OSA, but are not being treated.
- Article must present motor vehicle crash risk data in a manner that will allow ECRI Institute to calculate (directly or through imputation) effect-size estimates and confidence intervals.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted to avoid double-counting individuals.

Inclusion Criteria for Key Question 6

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which

this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)

- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more subjects.
- Article must have enrolled subjects aged ≥18.
- Studies were limited to individuals with OSA only (no central apneas).
- Studies that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- Article must describe a study that attempted to determine the length of time required following initiation of an effective treatment for individuals with OSA to reach a degree of improvement that would permit safe driving (as determined through indirect measures of crash risk; i.e., driving simulators or cognitive/psychomotor functioning) or to show improvement in the risk factors associated with OSA (i.e., disease severity, daytime sleepiness, SaO_2, blood pressure).
- Articles were limited to those whose follow-up times were two weeks or less for treatment with CPAP, medication, and oral appliances, and one month or less for treatment with surgery.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted to avoid double-counting individuals.

Inclusion Criteria for Key Question 7

- Article must have been published in the English language. Moher et al.(250) have demonstrated that exclusion of non-English language studies from meta-analyses has little impact on the conclusions drawn. Juni et al.(251) found that non-English studies typically were of lower methodologic quality and that excluding them had little effect on effect-size estimates in the majority of meta-analyses they examined. Although we recognize that in some situations exclusion of non-English studies could lead to bias, we believe that the few instances in which this may occur do not justify the time and cost typically necessary for translation of studies to identify those of acceptable quality for inclusion in our reviews.(250,251)
- Studies with a limited number of subjects - Case reports and trials with less than 10 subjects per arm were excluded.
- Studies were limited to individuals with OSA only (no central apneas).
- Studies that did not address the relationship between treatment noncompliance and/or treatment withdrawal and time to recurrence of increased crash risk in individuals with OSA were excluded.
- Trials that evaluated both OSA and other sleep disordered individuals were included as long as data for OSA subjects could be analyzed separately from that of other subject populations.
- All methods of measuring treatment compliance were considered valid for addressing this key question.

Appendix D: Excluded Articles

Table D-1. Excluded Studies (Key Question 1)

Reference	Year	Reason for Exclusion
Desai et al.(252)	2006	Simulated driving
Mazza et al.(154)	2006	Simulated driving
Pack et al.(47)	2006	Simulated driving and cognitive functioning
Pichel et al.(253)	2006	Simulated driving, no control group
Canani et al.(37)	2005	Does not evaluate sleep apnea
Goncalves et al.(254)	2004	No control group
Sforza et al.(255)	2004	Evaluated cognitive functioning
Desai et al.(256)	2003	Case reports
Ferini-Strambi et al.(257)	2003	Evaluated cognitive functioning
Powell et al.(258)	2002	Sleep apnea was self-reported and not confirmed with polysomnography
Yee et al.(259)	2002	Participants in study included those with periodic limb movements syndrome
Fulda and Schulz(260)	2001	Review
George, CFP(151)	2001	Used same participants as George and Smiley, 1999(75)
Hack et al.(161)	2001	Simulated driving
Turkington et al.(88)	2001	Simulated driving
Juniper et al.(261)	2000	Simulated driving
Masa et al.(262)	2000	Control group included some drivers with sleep apnea
Randerath et al.(263)	2000	Simulated driving, crash history not reported for individuals with sleep apnea
Risser et al.(264)	2000	Simulated driving
Yamamoto et al.(89)	2000	No control group. Examines accident rate following treatment with CPAP.
Findley et al.(265)	1999	Simulated driving
Hakkanen et al.(266)	1999	Examined blink duration as indicator of driver sleepiness, no crash data presented
Lojander et al.(183)	1999	Evaluated cognitive functioning
Teran-Santos et al.(267)	1999	Used same participants as Teran-Santos et al. 1999(76)
Barbe et al.(90)	1998	Used same participants as Barbe et al. 2006(68)
Noda et al.(91)	1998	Appropriate outcome data not presented for OSA and control groups
Krieger et al.(153)	1997	Study group not comparable to French population
Engleman et al.(92)	1996	No control group
George et al.(268)	1996	Simulated driving
George et al.(269)	1996	Simulated driving
Findley et al.(270)	1995	Simulated driving
Haraldsson et al.(175)	1995	Used same participants as Haraldsson et al. 1990(80)
Horne and Reyner(271)	1995	Did not investigate crashes caused by sleep apnea
Naegele et al.(272)	1995	Evaluated cognitive functioning
Stoohs R.(273)	1995	Used same participants as Stoohs et al. 1994(67)
Bedard et al.(274)	1993	Evaluated cognitive functioning
Flemons et al.(275)	1993	Abstract and simulated driving
Minemura et al.(276)	1993	Article in Japanese
Telakivi et al.(277)	1993	Evaluated cognitive functioning, no control group
Cheshire et al.(278)	1992	Evaluated cognitive functioning, no control group
Bedard et al.(279)	1991	Evaluated cognitive functioning, no control group

Reference	Year	Reason for Exclusion
Scheltens et al.(280)	1991	Case report
Haraldsson et al.(281)	1990	Simulated driving
Findley et al.(157)	1989	Simulated driving
Findley et al.(282)	1989	Letter to the editor
Gonzales-Rothi et al.(283)	1988	Crash data included individuals “who no longer operate a motor vehicle for fear of falling asleep at the wheel”
George et al.(284)	1987	Letter to the editor

CPAP = Continuous positive airway pressure; OSA = Obstructive sleep apnea.

Table D-2. Excluded Studies (Key Question 2)

Reference	Year	Reason for Exclusion
Desai et al.(252)	2006	Simulated driving
Mazza et al.(154)	2006	Simulated driving
Pack et al.(47)	2006	Simulated driving and cognitive functioning
Pichel et al.(253)	2006	Simulated driving, no control group
Canani et al.(37)	2005	Does not evaluate sleep apnea
Goncalves et al.(254)	2004	Does not evaluate risk factors and crash risk
Howard et al.(48)	2004	Appropriate outcome data not presented for individuals with OSA
Kingshott et al.(69)	2004	Appropriate outcome data not presented for individuals with OSA
Sforza et al.(255)	2004	Evaluated cognitive functioning
Desai et al.(256)	2003	Case reports
Ferini-Strambi et al.(257)	2003	Evaluated cognitive functioning
Powell et al.(258)	2002	Sleep apnea was self-reported and not confirmed with polysomnography
Yee et al.(259)	2002	Participants in study included those with periodic limb movements syndrome
Fulda and Schulz(260)	2001	Review
George(151)	2001	Used same participants as George and Smiley, 1999(75)
Hack et al.(161)	2001	Simulated driving
Juniper et al.(261)	2000	Simulated driving
Lloberes et al.(74)	2000	Appropriate outcome data not presented for individuals with OSA
Masa et al.(262)	2000	Appropriate outcome data not presented
Randerath et al.(263)	2000	Simulated driving, crash history not reported for individuals with sleep apnea
Risser et al.(264)	2000	Simulated driving
Findley et al.(265)	1999	Simulated driving
Hakkanen et al.(266)	1999	Examined blink duration as indicator of driver sleepiness, no crash data presented
Lojander et al.(183)	1999	Evaluated cognitive functioning
Teran-Santos et al.(262)	1999	Appropriate outcome data not presented
Teran-Santos et al.(267)	1999	Used same participants as Teran-Santos et al. 1999(76)
Krieger et al.(153)	1997	Accidents included domestic accidents, work accidents, and other-unspecified
Young et al.(77)	1997	Appropriate outcome data not presented
George et al.(268)	1996	Simulated driving
George et al.(269)	1996	Simulated driving
Findley et al.(270)	1995	Simulated driving
Horne and Reyner(271)	1995	Did not investigate crashes caused by sleep apnea
Naegele et al.(272)	1995	Evaluated cognitive functioning
Stoohs R.(273)	1995	Used same participants as Stoohs et al. 1994(67)
Bedard et al.(274)	1993	Evaluated cognitive functioning
Flemons et al.(275)	1993	Abstract and simulated driving
Minemura et al.(276)	1993	Article in Japanese
Telakivi et al.(277)	1993	Evaluated cognitive functioning, no control group
Cheshire et al.(278)	1992	Evaluated cognitive functioning, no control group
Bedard et al.(279)	1991	Evaluated cognitive functioning, no control group
Scheltens et al.(280)	1991	Case report

Reference	Year	Reason for Exclusion
Haraldsson et al.(80)	1990	Appropriate outcome data not presented
Haraldsson et al.(281)	1990	Simulated driving
Findley et al.(157)	1989	Simulated driving
Findley et al.(282)	1989	Letter to the editor
Gonzales-Rothi et al.(283)	1988	Crash data included individuals "who no longer operate a motor vehicle for fear of falling asleep at the wheel"
George et al.(284)	1987	Letter to the editor

OSA = Obstructive sleep apnea.

Table D-3. Excluded Studies (Key Question 3)

Reference	Year	Reason for exclusion
Moller et al.(285)	2006	Background information.
Nabi et al.(286)	2006	Background information.
Nolan et al.(249)	2006	Not relevant.
Kingshott et al.(69)	2004	Mixed study population.
Belz et al.(287)	2004	Commercial drivers without OSA/Background only.
Lardelli-Claret et al.(288)	2003	Background only.
Randerath et al.(209)	2002	Not relevant.
Juni et al.(251)	2002	Background Information to exclude non-English publications.
Monasterio et al.(187)	2001	ESS data are presented for the whole sample, but MSLT was only conducted on a subgroup. Therefore, no comparison is possible.
Randerath et al.(289)	2001	Not relevant.
Randerath et al.(263)	2000	Not relevant.
Moher et al.(250)	2000	Background information to exclude non-English publications.
Chervin et al.(86)	1999	Mixed population.
Benbadis et al.(290)	1999	Mixed population.
Bennett et al.(291)	1999	Mixed population.
Reyner and Horne(292)	1998	Background information.
Bennett et al.(293)	1998	Mixed population.
Olson et al.(294)	1998	Mixed population.
Hers et al.(295)	1997	Not relevant.
Chervin et al.(296)	1997	Mixed population.
Johns(297)	1993	No objective sleepiness measure.
McEnvoy and Thornton(298)	1984	Not relevant.

ESS = Epworth Sleepiness Scale; MSLT = Multiple sleep latency test; OSA = Obstructive sleep apnea.

Table D-4. Excluded Studies (Key Question 4)

Study	Year	Reason for exclusion
Ancoli-Israel et al.(299)	1997	Study included healthy subjects (spectrum bias)
Arand et al.(300)	2005	Review article
Ayappa et al.(301)	2004	Study included healthy subjects (spectrum bias)
Ayas et al.(302)	2003	Study included subjects without sleep apnea
Bagnato et al.(303)	2000	Study included individuals under 18 years of age
Ballester et al.(304)	2000	Study included subjects recruited from the general population
Bar et al.(305)	2003	Study included healthy subjects (spectrum bias)
Bonsignore et al.(306)	1990	Study included individuals with other disorders
Cooper et al.(307)	1991	Age of participants not recorded
Dingli et al.(308)	2003	Does not report sensitivity and specificity
Furuta et al.(108)	1999	Does not report sensitivity and specificity
Gagnadoux et al.(309)	2002	Does not report sensitivity and specificity
Gyulay et al.(310)	1987	Study included one subject with central sleep apnea
Hakkanen et al.(266)	1999	Does not report sensitivity and specificity
Harma et al.(311)	1998	<10 subjects in study, all healthy volunteers
Iber et al.(312)	2004	Does not report sensitivity and specificity
Johns et al.(84)	1991	Does not report sensitivity and specificity
Kingshott et al.(110)	1995	Does not report sensitivity and specificity
Man et al.(313)	1995	Study included individuals under 18 years of age
Orr et al.(314)	1994	Age of participants not recorded
Osman et al.(315)	1999	Does not report sensitivity and specificity
Overland et al.(316)	2005	Does not report sensitivity and specificity
Penzel et al.(317)	2004	Does not report sensitivity and specificity
Pepin et al.(318)	1991	Study included individuals with other disorders
Pillar et al.(319)	2003	Study included healthy subjects (spectrum bias)
Portier et al.(320)	2000	Does not report sensitivity and specificity
Rauscher et al.(321)	1991	Does not report sensitivity and specificity
Redline et al.(322)	1991	Does not report sensitivity and specificity
Rees et al.(323)	1998	Does not report sensitivity and specificity
Suzuki et al.(324)	2000	Does not report sensitivity and specificity
Van Surell et al.(325)	1995	Study included mixed population
Westbrook et al.(326)	2005	Study included healthy subjects (spectrum bias)
Whittle et al.(327)	1997	Does not report sensitivity and specificity
Williams et al.(328)	1991	Does not report sensitivity and specificity
Wiltshire et al.(329)	2001	Age of participants not recorded
Yin et al.(329)	2005	Study included individuals under 18 years of age

Table D-5. Excluded Studies (Key Question 5)

Reference	Year	Reason for Exclusion
Findley et al.(330)	1992	Review
Findley et al.(331)	2000	Abstract
Minemura et al.(276)	1993	Japanese language
Gonzalex-Roth et al.(283)	1998	Does not address Key Question 5
Engleman et al.(109)	1997	Does not address Key Question 5/crash
Rauscher et al.(332)	1993	Not a randomized controlled trial
Loube et al.(333)	1997	Outcome irrelevant
Jokic et al.(334)	1999	No relevant control group
V-Flores et al.(208)	1996	Not a randomized controlled trial
Meurice et al.(335)	1996	Not a randomized controlled trial
Teschler et al.(336)	1996	No relevant control group
Feuerstein et al.(337)	1997	Not a randomized controlled trial
Engleman et al.(109)	1997	Not a randomized controlled trial
Meurice et al.(338)	1998	No relevant control group
Ficker et al.(339)	1998	Not a randomized controlled trial
Piccirillo et al.(340)	1998	Not a randomized controlled trial
Hoy et al.(341)	1999	No relevant control group
Stefanescu et al.(342)	2003	Not relevant to Key Question 5
Engleman et al.(343)	1993	Not a randomized controlled trial
Bedard et al.(274)	1993	Not a randomized controlled trial
Kribbs et al.(107)	1993	Not a randomized controlled trial
Restrick et al.(344)	1993	Not Obstructive Sleep Apnea
Kribbs et al.(345)	1993	Not a randomized controlled trial
Montplaisir et al.(346)	1992	Not a randomized controlled trial
Findley et al.(330)	1992	Review
Palmer et al.(347)	2004	No relevant control group
Kessler et al.(348)	2003	Not a randomized controlled trial
Randerath et al.(263)	2000	Not a randomized controlled trial
Douglas et al.(349)	2000	Review article
Yamamoto et al.(89)	2000	Not a randomized controlled trial
Hakkanen et al.(266)	1999	Not a randomized controlled trial
Cassel et al.(78)	1996	Not a randomized controlled trial
Scharf et al.(152)	1999	Not a randomized controlled trial
Hui et al.(350)	2000	No relevant control group
Hoy et al.(351)	1999	No relevant control group
Hoekema et al.(352)	2006	Abstract
Blanco et al.(353)	2005	No relevant control group
Engleman et al.(354)	2002	No relevant control group
Kingshott et al.(355)	2000	Not a randomized controlled trial
Jenkinson et al.(356)	1997	Not a randomized controlled trial
Stamnitz et al.(357)	2004	No relevant control group
Tan et al.(358)	2002	No relevant control group

Reference	Year	Reason for Exclusion
Gotsopoulos et al.(359)	2002	Not a randomized controlled trial
Munoz et al.(360)	2000	Not a randomized controlled trial
Sanchez et al.(361)	2004	Not a randomized controlled trial
Ferini et al.(257)	2003	Not a randomized controlled trial
Puhan et al.(362)	2005	Not a standard treatment
Marshall et al.(363)	2005	No relevant control group
Roizenblatt et al.(364)	2006	Single dose study
Bailey et al.(365)	2005	Review
Dort et al.(366)	2004	Survey
Coughlin et al.(367)	2004	Abstract
Randerath et al.(209)	2002	No relevant control group
Baker et al.(368)	2003	Abstract
Egea et al.(369)	2004	Abstract
Lam et al.(370)	2003	Abstract
Vgontzas et al.(371)	2003	Treatment group too small
Saletu et al.(210)	1999	Not a randomized controlled trial
Berry et al.(372)	1995	Single dose study
Issa et al.(373)	1992	Treatment group too small
Hanzel et al.(374)	1991	No relevant control group
Stepanski et al.(375)	1988	Treatment group too small
Suratt et al.(376)	1986	Single dose study
Rubin et al.(377)	1986	Case series
Guillemin et al.(378)	1983	Before-After
Brownell et al.(379)	1983	Treatment group too small
Kumar et al.(380)	2004	Review
Boyd et al.(381)	2006	Review
Schwartz et al.(382)	2005	Review
Walsh et al.(383)	1995	Case series
Ferber et al.(211)	1993	Single dose study
Cross et al.(384)	2006	No relevant control group
West et al.(385)	2006	No relevant control group
Duong et al.(386)	2005	Follow-up time too short
Resta et al.(387)	2004	No relevant control group
Noseda et al.(388)	2004	No relevant control group
Marrone et al.(237)	2004	No relevant control group
Randerath et al.(389)	2003	No relevant control group
Wiest et al.(203)	2002	No relevant control group
Johasz et al.(390)	2001	No relevant control group
Ficker et al.(205)	2000	No relevant control group
Hudgel et al.(391)	2000	No relevant control group
Teschler et al.(206)	2000	No relevant control group
Pepin et al.(392)	1999	No relevant control group
Kessler et al.(393)	2003	Follow-up time too short

Reference	Year	Reason for Exclusion
Konnerman et al.(394)	1998	No relevant control group
Kushida et al.(395)	2006	Protocol
Malik et al.(396)	2004	Not a randomized controlled trial
Sanders et al.(397)	2002	Review
Choi et al.(398)	2001	No relevant data
Randerath et al.(204)	2001	No relevant control group
Farre et al.(399)	1999	Study not relevant
Hoster et al.(400)	1997	German language
Ficker et al.(401)	1997	German language
Dixon et al.(402)	2005	Before-After
Hong et al.(403)	2003	Study not relevant
Hsu et al.(404)	2007	No relevant control group
Lin et al.(405)	2006	Not a randomized controlled trial
De Luca et al.(406)	2006	Review
Kezirian et al.(407)	2006	Review
Thuler et al.(408)	2002	Portuguese language
Hattori et al.(409)	2003	Not a randomized controlled trial
Finkelstein et al.(410)	1997	No relevant control group
Bardwell et al.(411)	2007	No relevant outcome
Freire et al.(412)	2007	Not a standard treatment

Table D-6. Excluded Studies (Key Question 6)

Reference	Year	Reason for Exclusion
Rauscher et al.(332)	1993	Follow-up time greater than 2 weeks
Suratt et al.(413)	1992	Follow-up time greater than 1 month
Schwartz et al.(197)	1991	Follow-up time greater than 1 month
Pasquali et al.(414)	1990	Follow-up time greater than 1 month
Rubinstein et al.(415)	1988	Follow-up time greater than 1 month
Suratt et al.(416)	1987	Less than 10 individuals per group
Smith et al.(417)	1985	Follow-up time greater than 1 month
Harman et al.(418)	1982	Less than 10 individuals per group
Loube et al.(333)	1997	Outcomes of interest not reported
Stradling et al.(419)	1998	Outcomes of interest not reported
Sher et al.(41)	1996	Review article
Schmidt-Nowara et al.(44)	1995	Review article
Jokic et al.(334)	1999	Follow-up time greater than 2 weeks
Lojander et al.(182)	1996	Follow-up time greater than 2 weeks
Findley et al.(157)	1989	Follow-up time greater than 2 weeks
Meurice et al.(335)	1996	Follow-up time greater than 2 weeks
Engleman et al.(172)	1996	Follow-up time greater than 2 weeks
Teschler et al.(336)	1996	Follow-up time greater than 2 weeks
Engleman et al.(105)	1997	Follow-up time greater than 2 weeks
George et al.(156)	1997	Follow-up time greater than 2 weeks
Feuerstein et al.(337)	1997	Follow-up time greater than 2 weeks
Engleman et al.(109)	1997	Follow-up time greater than 2 weeks
Meurice et al.(338)	1998	Follow-up time greater than 2 weeks
Engleman et al.(104)	1998	Follow-up time greater than 2 weeks
Ficker et al.(339)	1998	Less than 10 individuals per group
Engleman et al.(103)	1999	Follow-up time greater than 2 weeks
Piccirillo et al.(340)	1998	Follow-up time greater than 1 month
Hoy et al.(341)	1999	Follow-up time greater than 2 weeks
Stefanescu et al.(342)	2003	Evaluated CPAP treatment on infants
Dinges and Weaver(420)	2003	Follow-up time greater than 2 weeks
Kajaste et al.(421)	2004	Follow-up time greater than 2 weeks
Engleman et al.(173)	1994	Follow-up time greater than 2 weeks
Engleman et al.(343)	1993	Follow-up time greater than 2 weeks
Bedard et at.(274)	1993	Follow-up time greater than 2 weeks
Kribbs et al.(107)	1993	Follow-up time greater than 2 weeks
Restrick et al.(344)	1993	Individuals did not have obstructive sleep apnea
Kribbs et al.(345)	1993	Outcomes of interest not reported
Montplaisir et al.(346)	1992	Follow-up time greater than 2 weeks
Findley et al.(330)	1992	Review article
Haroldsson et al.(422)	1991	Follow-up time greater than 1 month
Palmer et al.(347)	2004	Follow-up time greater than 2 weeks
Kessler et al.(348)	2003	Outcomes of interest not reported

Reference	Year	Reason for Exclusion
Hack et al.(161)	2001	Outcomes of interest not reported
George(151)	2001	Follow-up time greater than 2 weeks
Randerath et al.(263)	2000	Outcomes of interest not reported
Douglas and Engleman(349)	2000	Review article
Horstmann et al.(73)	2000	Follow-up time greater than 2 weeks
Yamamoto et al.(89)	2000	Follow-up time greater than 2 weeks
Findley et al.(72)	2000	Follow-up time greater than 2 weeks
Hack et al.(162)	2000	Follow-up time greater than 2 weeks
Hakkanen et al.(266)	1999	Follow-up time greater than 2 weeks
Cassel et al.(78)	1996	Follow-up time greater than 2 weeks
Engleman et al.(92)	1996	Follow-up time greater than 2 weeks
Findley et al.(423)	1990	Follow-up time greater than 2 weeks
Findley et al.(331)	2000	Abstract
Nussbaumer et al.(218)	2006	Follow-up time greater than 2 weeks
Scharf et al.(152)	1999	Follow-up time greater than 2 weeks
Krieger et al.(153)	1997	Follow-up time greater than 2 weeks
Minemura et al.(276)	1993	Article in Japanese
Giles et al.(424)	2006	Review article
Barnes et al.(166)	2004	Follow-up time greater than 2 weeks
Hui et al.(350)	2000	Follow-up time greater than 2 weeks
Hoy et al.(351)	1999	Follow-up time greater than 2 weeks
Hoekema et al.(352)	2006	Review article
Ryan et al.(195)	2005	Follow-up time greater than 2 weeks
Woodson et al.(199)	2003	Follow-up time greater than 2 weeks
Chaklravorty et al.(170)	2002	Outcomes of interest not reported
Engleman et al.(354)	2002	Follow-up time greater than 2 weeks
McArdle and Douglas(186)	2001	Follow-up time greater than 2 weeks
Kingshott et al.(355)	2000	Follow-up time greater than 2 weeks
Jenkinson et al.(356)	1997	Follow-up time greater than 2 weeks
Walker-Engstrom et al.(425)	2002	Follow-up time greater than 1 month
Barbe et al.(99)	2001	Follow-up time greater than 2 weeks
Steward et al.(426)	2005	Follow-up time greater than 1 month
Steward et al.(427)	2004	Follow-up time greater than 1 month
Stammnitz et al.(357)	2004	Outcomes of interest not reported
Tan et al.(358)	2002	Follow-up time greater than 1 month
Gotsopoulos et al.(359)	2002	Follow-up time greater than 2 weeks
Monasterio et al.(187)	2001	Follow-up time greater than 2 weeks
Montserrat et al.(188)	2001	Follow-up time greater than 2 weeks
Faccenda et al.(216)	2001	Follow-up time greater than 2 weeks
Munoz et al.(360)	2000	Follow-up time greater than 2 weeks
Arnulf et al.(428)	1997	Less than 10 individuals per group
Barbe et al.(68)	2006	Follow-up time greater than 2 weeks
Sanchez et al.(361)	2004	Follow-up time greater than 2 weeks

Reference	Year	Reason for Exclusion
Ferini-Stambi et al.(257)	2003	Follow-up time greater than 2 weeks
Lojander et al.(183)	1999	Follow-up time greater than 2 weeks
Puhan et al.(362)	2005	Evaluated didgeridoo playing as a treatment for obstructive sleep apnea
Marshall et al.(363)	2005	Follow-up time greater than 2 weeks
Henke et al.(177)	2001	Follow-up time greater than 2 weeks
Hirshkowitz et al.(178)	2007	Follow-up time greater than 2 weeks
Mazza et al.(154)	2006	Follow-up time greater than 2 weeks
Roizenblatt et al.(364)	2006	Medication not a treatment for obstructive sleep apnea
Hoekema et al.(155)	2006	Follow-up time greater than 2 weeks
Bailey(365)	2005	Review article
Dort(366)	2004	Evaluated CPAP compliance
Sundaram et al.(46)	2007	Review article
Coughlin et al.(367)	2004	Abstract
Kaneko et al.(181)	2003	Follow-up time greater than 2 weeks
Becker et al.(167)	2003	Follow-up time greater than 2 weeks
Pepperell et al.(193)	2001	Follow-up time greater than 2 weeks
Balcerzak and Przybylowski(368)	2003	Abstract
Egea et al.(369)	2004	Abstract
Li and Chen(370)	2003	Abstract
CADTH(429)	2007	Review article
Walker et al.(430)	2006	Follow-up time greater than 1 month
Nordgard et al.(431)	2006	Follow-up time greater than 1 month
Friedman et al.(432)	2006	Follow-up time greater than 1 month
Roth et al.(224)	2006	Follow-up time greater than 2 weeks
Vgontzas et al.(371)	2004	Follow-up time greater than 2 weeks
Berry et al.(372)	1995	Medication not a treatment for obstructive sleep apnea
Issa(373)	1992	Less than 10 individuals per group
Hanzel et al.(374)	1991	Follow-up time greater than 2 weeks
Stepanski et al.(375)	1988	Less than 10 individuals per group
Suratt et al.(376)	1986	Less than 10 individuals per group
Rubin et al.(377)	1986	Follow-up time greater than 2 weeks
Guilleminault and Hayes(378)	1983	Follow-up time greater than 2 weeks
Brownell et al.(379)	1983	Less than 10 individuals per group
Kumar(380)	2004	Review article
McMahon et al.(433)	2003	Review article
Hoekema et al.(434)	2004	Review article
Ayas et al.(233)	2004	Review article
Boyd et al.(381)	2006	Review article
Schwartz(382)	2005	Review article
Hedner et al.(435)	1996	Follow-up time greater than 2 weeks
Walsh et al.(383)	1995	Follow-up time greater than 2 weeks
Cross et al.(384)	2006	Outcomes of interest not reported
Hui et al.(179)	2006	Follow-up time greater than 2 weeks

Reference	Year	Reason for Exclusion
Campos-Rodrigez et al.(168)	2006	Follow-up time greater than 2 weeks
Robinson et al.(192)	2006	Follow-up time greater than 2 weeks
West et al.(385)	2006	Follow-up time greater than 2 weeks
Duong et al.(386)	2005	Outcomes of interest not reported
Usui et al.(198)	2005	Follow-up time greater than 2 weeks
Resta et al.(387)	2004	Follow-up time greater than 2 weeks
Noseda et al.(388)	2004	Follow-up time greater than 2 weeks
Marrone et al.(237)	2004	Follow-up time greater than 2 weeks
Mansfield et al.(185)	2004	Follow-up time greater than 2 weeks
Randerrath et al.(389)	2003	Follow-up time greater than 2 weeks
Barnes et al.(98)	2002	Follow-up time greater than 2 weeks
Juhasz et al.(390)	2001	Follow-up time greater than 2 weeks
Hudgel and Fung(391)	2000	Follow-up time greater than 2 weeks
Pepin et al.(392)	1999	Follow-up time greater than 2 weeks
Kessler et al.(393)	2003	Outcomes of interest not reported
Jenkinson et al.(180)	1999	Follow-up time greater than 2 weeks
Ballester et al.(164)	1999	Follow-up time greater than 2 weeks
Konermann et al.(394)	1998	Follow-up time greater than 2 weeks
Kushida et al.(395)	2006	Follow-up time greater than 2 weeks
Malik and Kenyon(396)	2004	Follow-up time greater than 2 weeks
Sanders(397)	2002	Review article
Choi et al.(398)	2001	Follow-up time greater than 2 weeks
Farre et al.(399)	1999	Outcomes of interest not reported
Chai et al.(234)	2007	Review article
Smith et al.(436)	2006	Review article
Schneerson and Wright(437)	2001	Review article
Lim et al.(438)	2007	Review article
Newman et al.(439)	2005	Follow-up time greater than 1 month
Young et al.(439)	2005	Review article
Dixon et al.(402)	2005	Follow-up time greater than 1 month
Lequex et al.(440)	2005	Follow-up time greater than 1 month
Peppard et al.(441)	2004	Evaluated exercise
Hong and Dimsdale(403)	2003	Evaluated physical activity and fatigue
Peppard et al.(191)	2000	Follow-up time greater than 1 month
Sampol et al.(196)	1988	Follow-up time greater than 1 month
Lojander et al.(442)	1988	Follow-up time greater than 1 month
Kansanen et al.(443)	1998	Follow-up time greater than 1 month
Kaleth et al.(444)	2007	Not relevant to this question
Hsu et al.(404)	2007	Follow-up time greater than 1 month
Friedman et al.(445)	2005	Follow-up time greater than 1 month
Lin et al.(405)	2006	Follow-up time greater than 1 month
DeLuca et al.(406)	2006	Review article
Cincik et al.(446)	2006	Primary snoring, not sleep apnea

Reference	Year	Reason for Exclusion
Kezirian et al.(407)	2006	Review article
Han et al.(447)	2005	Follow-up time greater than 1 month
Jiang et al.(448)	2004	Follow-up time greater than 1 month
Thuler et al.(408)	2002	Article in Portuguese
Hattori et al.(409)	2003	Case reports
Isono et al.(449)	2003	Follow-up time greater than 1 month
Ferguson et al.(174)	2003	Follow-up time greater than 1 month
Lysdahl and Haraldsson(450)	2002	Follow-up time greater than 1 month
Finkelstein et al.(451)	2002	Follow-up time greater than 1 month
Boudewyns et al.(452)	2001	Follow-up time greater than 1 month
Millman et al.(453)	2000	Follow-up time greater than 1 month
Ryan and Love(454)	2000	Follow-up time greater than 1 month
Bridgman and Dunn(455)	2000	Review article
Walker et al.(456)	1999	Follow-up time greater than 1 month
Remacle et al.(457)	1999	Outcomes of interest not reported
Mickelson and Ahuja(458)	1999	Follow-up time greater than 1 month
Isberg et al.(459)	1998	Outcomes of interest not reported
Woodson et al.(460)	1997	Outcomes of interest not reported
Finkelstein et al.(410)	1997	Outcomes of interest not reported
Janson et al.(461)	1997	Follow-up time greater than 1 month
Lojander et al.(182)	1996	Follow-up time greater than 1 month
Cahali et al.(462)	2004	Follow-up time greater than 1 month
Alajmi et al.(463)	2007	Review article
Bardwell et al.(411)	2007	Follow-up time greater than 2 weeks
Coughlin et al.(171)	2007	Follow-up time greater than 2 weeks
Freire et al.(412)	2007	Evaluated acupuncture as a treatment for obstructive sleep apnea
Phillips et al.(464)	1990	Less than 10 individuals per group
Cirignotta et al.(465)	1988	Medication not used to treat obstructive sleep apnea
Gonzalez-Rothi et al.(283)	1988	Outcomes of interest not reported
Reeves-Hoche et al.(466)	1995	Follow-up time greater than 2 weeks
Haraldsson et al.(163)	1995	Follow-up time greater than 1 month
Haroldsson et al.(175)	1995	Follow-up time greater than 1 month
Engleman et al.(109)	1997	Follow-up time greater than 2 weeks
Meston et al.(467)	2003	Outcomes of interest not reported
Oki et al.(468)	1999	Outcomes of interest not reported
Strobel et al.(96)	1996	Review article

CPAP = Continuous positive airway pressure.

Table D-7. Excluded Studies (Key Question 7)

Reference	Year	Reason for Exclusion
Weil et al.(469)	1987	Background information.
Collop et al.(470)	1991	Background information; no data on crash or indirect driving measures.
Issa and Sullivan(471)	1986	Not relevant to key question.
Ryan et al.(472)	1991	Background information.
Strohl et al.(473)	1986	Background information.
Barone-Kribbs et al.(474)	1993	Background information.
Barone-Kribbs et al.(345)	1993	Background information.
Diabetes Prevention Program Research Group(475)	2002	Background information.
Hartenbaum et al.(23)	2006	Background information.
Ellen et al.(476)	2006	Background information.
Packham and Ebden(477)	2000	Background information.
Young et al.(18)	2002	Background information.
Montserrat et al.(17)	2002	Background information.
Nilius et al.(240)	2006	Background information.
Caples et al.(20)	2005	Background information.
Riviere et al.(478)	2006	Non-English language article.
Franklin et al.(479)	1992	Non-English language article.
Greenham-Conway(480)	2003	Dissertation abstract – order cancelled.
Sin et al.(481)	2002	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
McMahon et al.(433)	2003	Background information.
Pelletier-Fleury et al.(229)	2001	Background information.
Meurice et al.(243)	2007	Background information.
Hoffstein(482)	2007	Background information.
Waldhorn et al.(226)	1990	Background information.
Fletcher and Luckett(483)	1991	Reported on in a systematic review, so results are not discussed separately.
Smith et al.(246)	2006	Background information.
Mortimore et al.(484)	1997	Background information.
Issa(373)	1991	Reported on in a systematic review, so not discussed separately.
Ball et al.(225)	2001	Background information.
Hussain et al.(235)	2004	Background information.
Means et al.(485)	2004	Background information.
Aloia et al.(486)	2001	Reported on in a systematic review, so results are not discussed separately.
Aloia et al.(241)	2005	Background information.
Anttalainen et at.(487)	2007	Not relevant.
Scharf et al.(488)	2004	Background information.
Stepnowsky and Dimsdale(489)	2002	Background information.
Hers et al.(295)	1997	Background information.
Fitzpatrick et al.(490)	2002	Reported on in a systematic review, so results are not reported separately.
McEnvoy and Thornton(298)	1984	Background information/excluded because of small sample size and no data on crash or indirect crash measures.
Chervin et al.(491)	1997	Included in a systematic review, so results are not discussed separately.

Reference	Year	Reason for Exclusion
Rauscher et al.(492)	1991	Background information/no data on crash or indirect measures of crash.
Schmidt-Nowara et al.(44)	1995	Background information.
Kripalani et al.(493)	2007	Systematic review, no OSA articles included.
Tjin et al.(494)	2001	Background information.
Weaver et al.(230)	1997	Background information.
Gagnadoux et al.(495)	1999	Study was excluded from interventions to increase compliance systematic review so results are not reported on here.
Sanders et al.(496)	2000	Background information.
Issa et al.(497)	1987	Background information/data are insufficiently reported to include this study in our analysis.
Noseda et al.(498)	1996	Background information/no data on crash or indirect crash reported.
Smith et al.(436)	2007	Background information.
Issa et al.(499)	1985	Abstract only available.
Krueger et al.(500)	2005	Background information.
Chai et al.(234)	2007	Background information.
Shneerson and Wright(437)	2007	Background information.
Lim et al.(438)	2007	Background information.
Giles et al.(424)	2006	Background information.
Marshall et al.(363)	2005	Included in a systematic review, so results are not discussed separately.
Randerath et al.(289)	2001	Included in a systematic review, so results are not discussed separately.
Hui et al.(350)	2000	Included in a systematic review, so results are not discussed separately.
Hoy et al.(351)	1999	Included in a systematic review, so results are not discussed separately.
d'Ortho et al.(501)	2000	Included in a systematic review, so results are not discussed separately.
Haniffa et al.(232)	2004	Background information.
Collard et al.(502)	1992	Only abstract available.
DeMolles et al.(247)	2004	Background information.
Edinger et al.(228)	1994	Background information.
Campos-Rodriguez et al.(503)	2005	Not relevant.
Pepin et al.(392)	1999	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
Engleman et al.(504)	1994	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
Hui et al.(505)	2006	Background information.
Likar et al.(506)	1997	Not part of Haniffa systematic review, because it was not an RCT- not discussed separately.
Krieger(507)	1992	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
Massie et al.(393)	1999	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
Berry et al.(42)	2002	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
Ayas et al.(233)	2004	Background information.
Taylor et al.(248)	2006	Background information.
Bachour and Maasilta(231)	2004	Background information.
Beecroft et al.(508)	2003	Study was excluded from interventions to increase compliance systematic review, so results are not reported on here.
Brander et al.(215)	1998	Background information.
Doherty et al.(509)	2005	Not relevant.

Reference	Year	Reason for Exclusion
Littner et al.(510)	2005	Guideline/Background information.
Kushida et al.(511)	2006	Guideline/Background information.
Kushida et al.(512)	2006	Guideline/Background information.
SIGN(513)	2003	Guideline/Background information.
ICSI(514)	2006	Guideline/Background information.
Ferguson et al.(515)	1996	Unable to locate.
Reeves-Hoche et al.(222)	1994	Background information.
Sampol et al.(227)	2007	Background information.
Sullivan and Issa(516)	1985	Expert opinion, not relevant.
Bradshaw et al.(517)	2006	Background information.
Stepnowsky and Moore(518)	2003	Background information.
Wiese et al.(244)	2005	Background information.
Lindberg et al.(217)	2006	Background information.
Jokic et al.(519)	1998	Not relevant.
Hukins(236)	2004	Background information.
Zimmerman et al.(223)	2006	Background information.
Marrone et al.(237)	2004	Background information.
Mador et al.(242)	2005	Background information.
Massie and Hart(520)	2003	Included in a systematic review comparing interface devices for CPAP, so results are not presented separately.
Meslier et al.(521)	1998	Not relevant, examined compliant subjects only.
Rauscher et al.(220)	1993	Background information.
Nolan et al.(238)	2007	Background information.
Parthasarathy et al.(522)	2006	Background information.
Popescu et al.(219)	2001	Background information.
Rauscher et al.(221)	1991	Background information.
Sullivan et al.(523)	1984	Sample size too small for inclusion and analysis; data reported as a series of five case reports, only some of which report on the time period before a recurrence of symptoms after cessation of CPAP.
Ross(524)	1999	Abstract only available.
Durieux et al.(525)	1992	Provides guidelines, but newer guidelines are presented in this report.
Wiest et al.(526)	2001	Not relevant.
Lewis et al.(245)	2005	Background information.
Teschler et al.(527)	1997	Not relevant.
Krieger et al.(528)	1996	Not relevant.
Sullivan et al.(529)	1984	Not relevant.
Smith and Stradling(530)	2002	Subjects compliant with CPAP are randomized to either no treatment for 3 days followed by a trial with a mandibular advancement device (MAD) or vice versa. Cannot determine what the data in the tables represent and tables do not agree with text, so excluded this study from the analysis.
Sullivan et al.(531)	1983	Case series reports of 2 subjects; too small sample size for use in analysis.
Tyrrell et al.(532)	2006	Background information.
Van Dulmen et al.(533)	2007	Not relevant, systematic review of interventions to increase treatment adherence but included all diseases.

CPAP = Continuous positive airway pressure; OSA = Obstructive sleep apnea; RCT = Randomized controlled trial.

Appendix E: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI Institute evidence reports differ substantially from other systematic review in that we provide two types of conclusions; qualitative conclusions and quantitative conclusions. In order to reach these conclusions we use an algorithm developed by ECRI Institute to guide the conduct and interpretation of the analyses performed during the development of this evidence report.(49) The algorithm, which is presented in Figure E-3 through Figure E-6, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately the stability and strength-of-evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. Each of these sections, the decision points that fall within them, and the decision rules that were applied at each step in the present evidence report are described below.

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: (1) to assess the quality of each included study; and (2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study-quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used the ECRI Institute Quality Scale I (for randomized and nonrandomized comparative studies), the ECRI Institute Quality Scale III (for pre-post studies), and a revised version of the Newcastle-Ottawa Quality Assessment Scale (for case-control studies).(534) These instruments are presented in Appendix F.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key question's specific evidence base into one of three distinct categories: high, moderate, or low quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median EIQS Score	Median EIQS III Score	Median NOQAS Score	Median EQS VI Score
High Quality	≥9.0			
Moderate Quality	6.0 to 8.9	≥9.0	≥8.0	≥8.0
Low Quality	≤6.0	<9.0	<8.0	<9.0

EIQS= ECRI Institute Quality Scale; NQQAS = Newcastle-O'Harra quality assessment scale.

Decision Point 3: Quantitative Analysis Performed?

In this evidence report the answer to Decision Point 3 depended on a number of factors, including the number of available studies and the adequacy of reporting of study findings. For any given question, combinable data from at least 3 studies must be available before a quantitative analysis will be

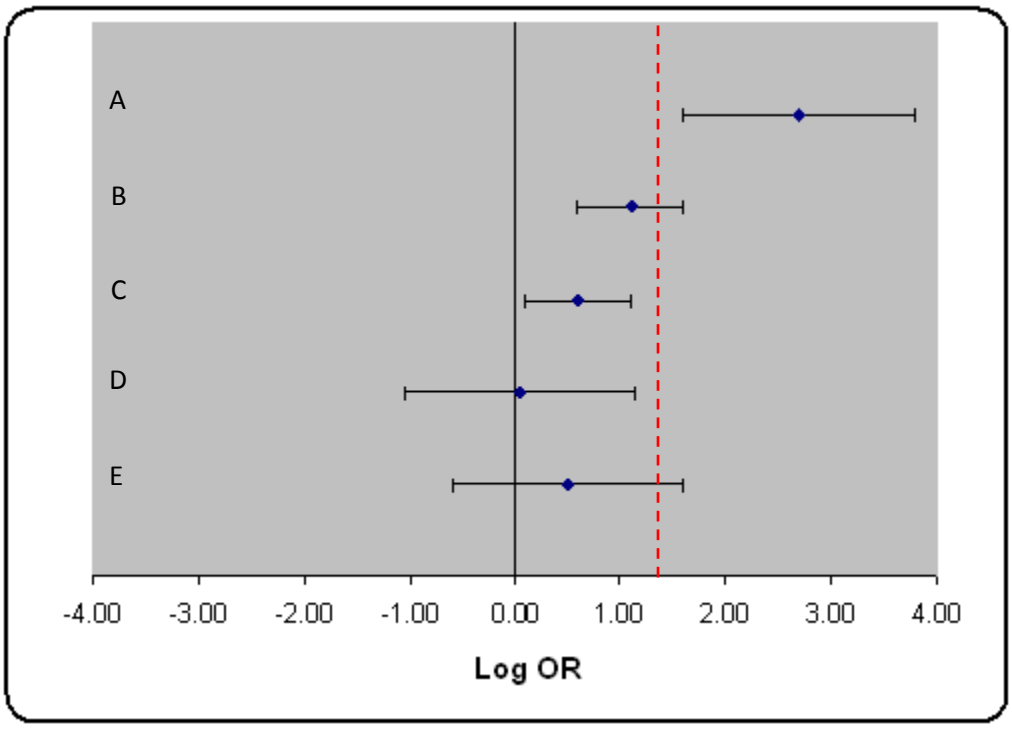
considered. If 4 or more studies were available but poor reporting precluded ECRI Institute from directly computing relevant effect-size estimates for >75% of the available studies, no quantitative analysis were performed. If no quantitative analyses were performed, we moved directly to Decision Point 8, which deals with the assessment of the available evidence with the aim of drawing a purely qualitative conclusion.

Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of homogeneity. For this evidence report we used both the Q-statistic and Higgins and Thompson's I^2 statistic.(8) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50% and *P*(Q) >0.10.

If the findings of the studies included were homogeneous (I^2 <50% and *P*(Q) >0.10), we obtained a summary effect-size estimate by pooling the results of these studies using fixed-effects meta-analysis. Having obtained a summary effect-size estimate, we then determined whether this estimate effect-size estimate was informative. That is, we determined whether the findings of the meta-analysis allowed a conclusion to be drawn. To see what is meant by this, consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is noninformative.

Figure E-1. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant; however, it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect, and it is also unclear whether the treatment effect is clinically important. This latter finding is thus noninformative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the fixed-effects meta-analysis were found to be informative, we next assessed the stability of the summary effect-size estimate obtained. Stability refers to the likelihood that a summary effect-size estimate will be substantially altered by changing the underlying assumptions of the analysis. Analyses that are used to test the stability of an effect-size estimate are known as sensitivity analyses. Clearly, ones confidence in the validity of a treatment effect-size estimate will be greater if sensitivity analyses fail to significantly alter the summary estimate of treatment effect.

For this evidence report, we utilized four different sensitivity analyses. These sensitivity analyses are:

1. *Random-effects meta-analysis of complete evidence base.* When the quantitative analysis is performed on a subset of available studies, a random-effects meta-analysis that includes imprecise estimates of treatment effect calculated for all available studies will be performed. For this evidence report, the summary estimate of treatment effect determined by this analysis will be compared to the summary effect-size estimate determined by the original fixed-effects meta-analysis. If the random-effects effect-size estimate differs from the original fixed-effects meta-analysis by some prespecified tolerance, the original effect-size estimate will not be considered stable.

   The prespecified tolerance levels for each of the potential effect-size estimates we could have utilized in this evidence report are presented in Table E-2.

Table E-2. Prespecified Tolerance Levels

Effect-Size Estimate	WMD	SMD	% of Individuals	RR	OR
Tolerance	+/-5%	+/-0.1	+/-5%	+/-0.05	+/-0.05

OR = Odds ratio; RR = Risk ratio; SMD = Standardized mean difference; WMD = Weighted-mean difference.

2. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.
3. *Publication bias test.* The publication bias test used in this evidence report was that of Duval and Tweedie.(12-14,65) Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(13,14) estimates the number of unpublished studies (and their effect-sizes). After addition of any "missing" data to the original meta-analysis, the overall effect-size is estimated again. If evidence of publication bias was identified and the summary effect-size estimate, adjusted for "missing" studies, differed from the pooled estimate of treatment effect determined by the original fixed-effects meta-analysis by >±5%, then we

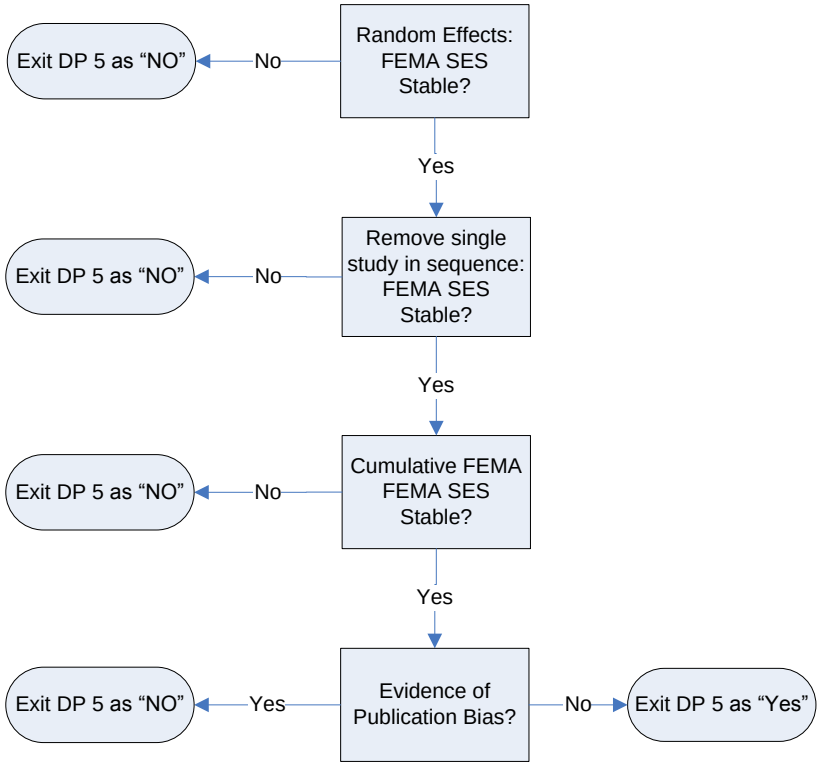
determined that the findings of our original analysis are not robust and the effect-size estimate is not stable.

4. *Cumulative fixed-effects meta-analysis.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect-size estimate. For this evidence report, we performed three different cumulative fixed-effects meta-analyses:
    a. Studies were added in order of weight
    b. Studies were added cumulatively to a fixed-effects meta-analysis by date of publication-oldest study first.
    c. Studies were added cumulatively to a fixed-effects meta-analysis by date-newest study first.

    In each instance, the pooled effect-size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect-size estimate effect of >±5%.

Because it is possible to reach Decision Point 6 with two different types of evidence bases (100% or <100% ≥75% of total available evidence base), two slightly different sets of sensitivity analyses are needed. Figure E-2 shows the procedural algorithm that was used when dealing with these two types of evidence bases.

Figure E-2. Sensitivity Analysis Algorithm 1: Used when Original Fixed-effects Meta-analysis Utilized Data from All Available Studies



Decision Points 6 and 7: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report we did not encounter any situations where we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 6 and 7 are irrelevant to the present report and we do not discuss them further.

Decision Point 8: Are Qualitative Findings Robust?

Decision Point 8 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. For this evidence report, a single sensitivity analysis was performed–a cREMA. We considered our qualitative findings to be overturned only when the findings of the cREMA altered our qualitative conclusion (i.e., a statistically significant finding became nonsignificant as studies were added to the evidence base). If the qualitative findings of the last three study additions were in agreement, then we concluded that our qualitative findings were robust.

Decision Point 9: Are Data Qualitatively Consistent?

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example, one might ask, "When compared to insulin injection, do all included studies find that inhaled insulin is a significant risk factor for a motor vehicle crash?"

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn one's qualitative conclusion.

The algorithm divides the magnitude of effect into two categories–large and not large. Determining the threshold above which the observed magnitude of effect can be considered to be large cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect-size estimate is "extremely large" using a modified Delphi technique.

Figure E-3. General Section

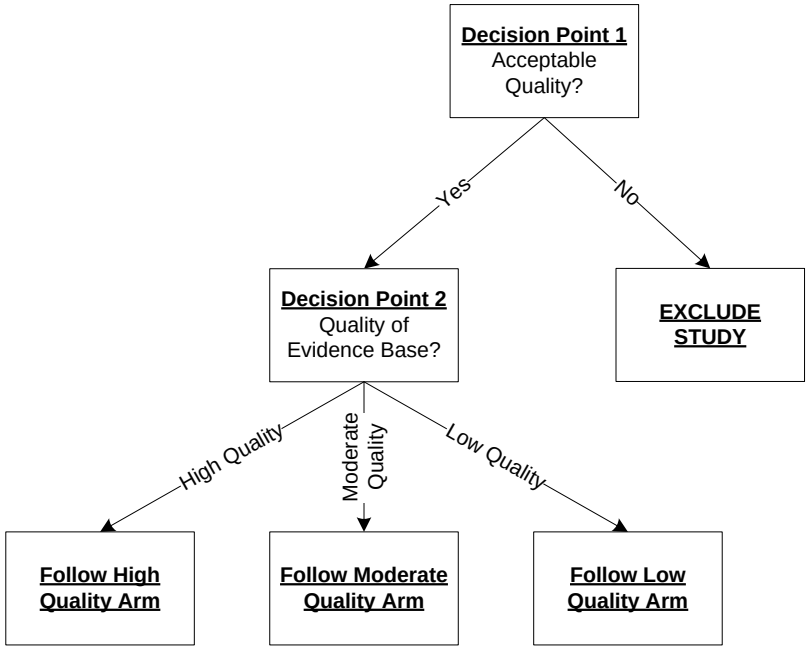


Figure E-4. High-quality Pathway

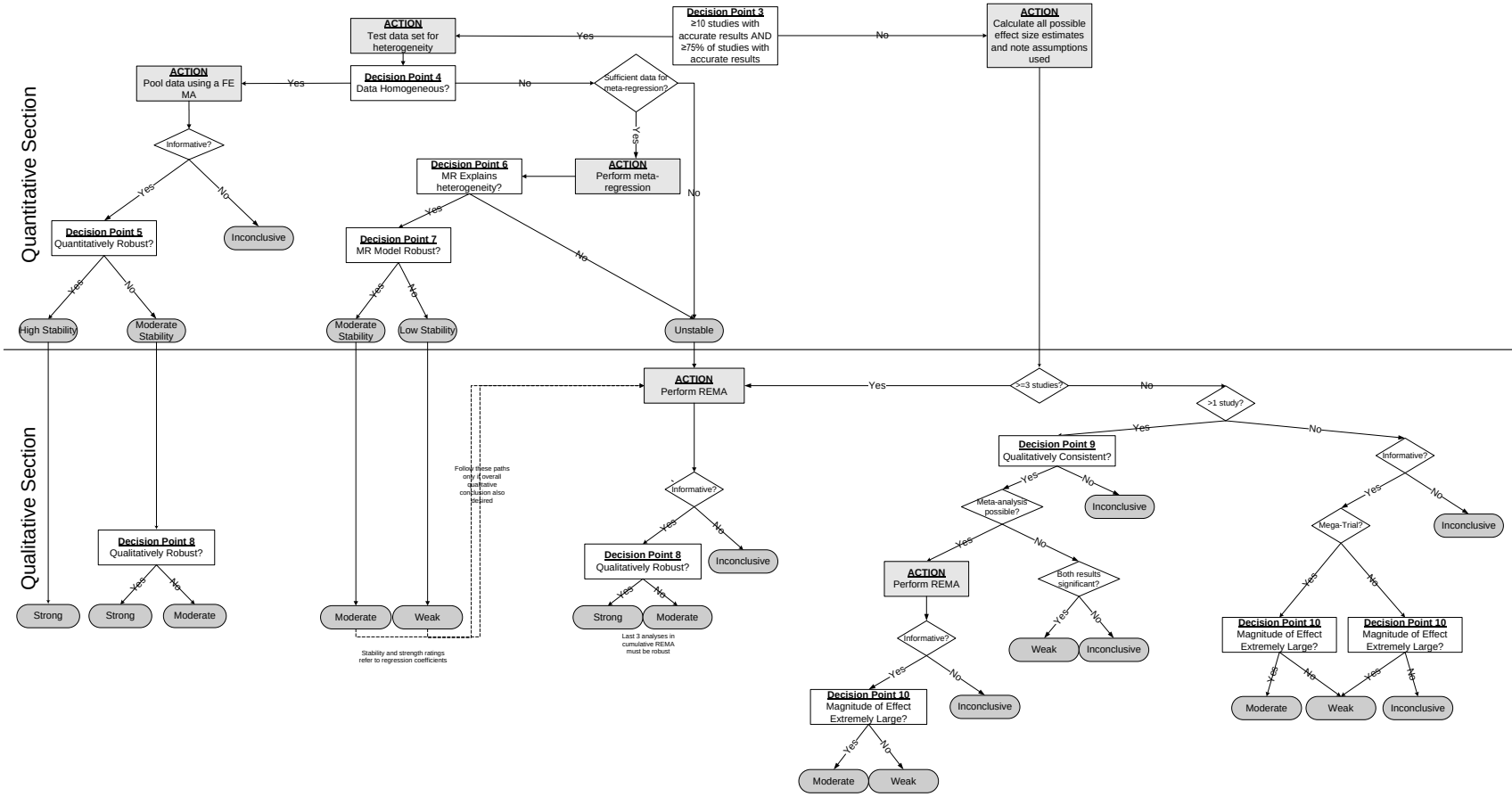


Figure E-5. Moderate-quality Pathway

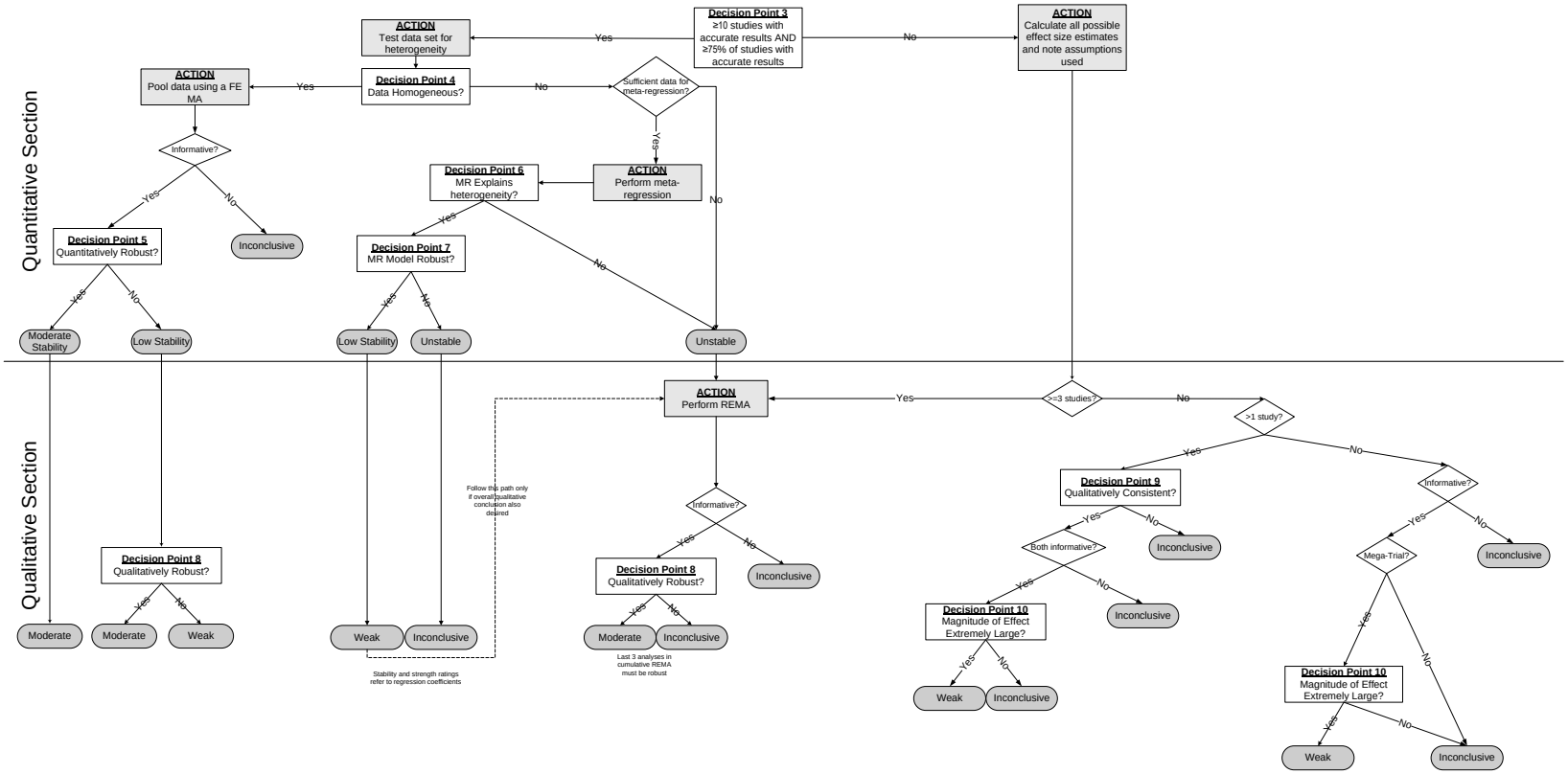
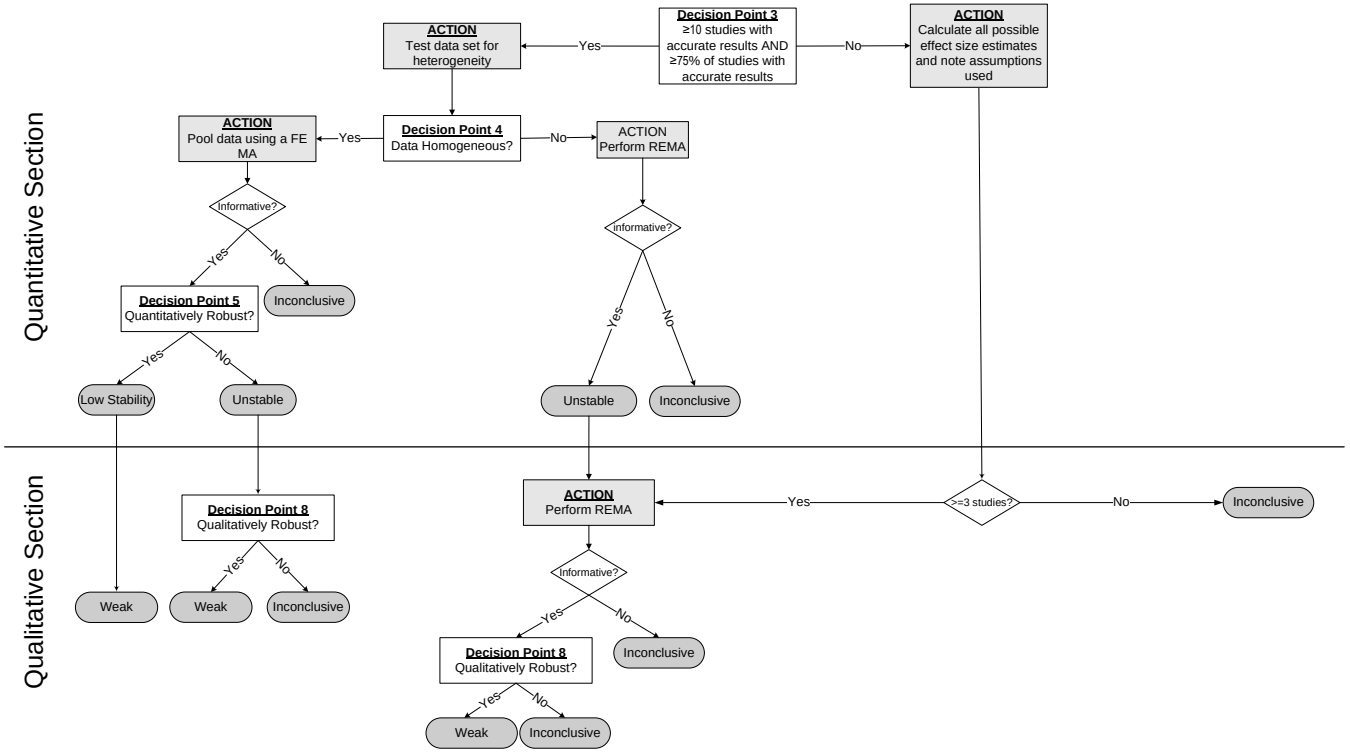


Figure E-6. Low-quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report: ECRI Institute Quality Scale I for comparative trials; ECRI Institute Quality Checklist III for before-after studies; and a revised version of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(534)

ECRI Institute Quality Scale I: Controlled Trials

Question #	Question
1	Were patients randomly assigned to the study's groups?
2	Did the study employ stochastic randomization?
3	Were any methods other than randomization used to make the patients in the study's groups comparable?
4	Were patients assigned to groups based on factors other than patient or physician preference?
5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
7	Was the comparison of interest prospectively planned?
8	Did ≥85% of the patients complete the study?
9	Was there a ≤15% difference in completion rates in the study's groups?
10	Were all of the study's groups concurrently treated?
11	Was compliance with treatment ≥85% in both of the study's groups?
12	Were all of the study's groups treated at the same center?
13	Were subjects blinded to the treatment they received?
14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
15	Was the treating physician blinded to the groups to which the patients were assigned?
16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
17	Was there concealment of allocation?
18	Was the outcome measure of interest objective **and** objectively measured?
19	Were the same laboratory tests, clinical findings, psychologic instruments, etc. used to measure the outcomes in all of the study's groups?
20	Was the instrument used to measure the outcome standard?
21	Was the same treatment given to all patients enrolled in the experimental group?
22	Was the same treatment given to all patients enrolled in the control group?
23	Were the follow-up times in all of the study's relevant groups approximately equal?
24	Was the funding for this study derived from a source that does not have a financial interest in its results?
25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section, supported by the data presented in the article's results section?

ECRI Institute Quality Scale III: Pre-Post Studies

Item	Question
1	Was the study prospective?
2	Did the study enroll all patients or consecutive patients?
3	Were the criteria for including and excluding patients based on objective laboratory and/or clinical findings?
4	Were the patient inclusion/ exclusion criteria established *a priori*?
5	Was the same initial treatment given to all patients enrolled?
6	Did all patients receive the same subsequent treatment(s)?
7	Was the outcome measure objective and objectively measured?
8	Did ≥85% of patients complete the study?
9	Were the characteristics of those who did and did not complete the study compared, and were these characteristics similar?
10	Was the funding for this study derived from a source that does not have a financial interest in its results?
11	Were the author's conclusions, as stated in the abstract or the article's discussion section, supported by the data presented in the article's results section?

ECRI Institute Quality Scale VI: Surveys

Item	Question
1	Were the questions developed from an expert group or focus group?
2	Was the pretest sample sufficiently large (>40 respondents)?
3	Were the characteristics of those who did not complete the study compared with those who completed the study, and were those characteristics similar?
4	Were the pretest sample respondents similar in characteristics to the study's respondents?
5	Were the respondents selected for the survey either consecutively or randomly?
6	Are the questions about crash (or other relevant outcome) not in the first 25% of the questions?
7	Does the questionnaire have reliability checks by asking the same question more than once but differently?
8	Were the respondents informed that their responses were confidential?
9	Were the conclusions as stated in the abstract and discussion consistent with the data presented in the results section?
10	Was the funding for this study derived from a source that does not have a financial interest in its results?

Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

The original Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies consisted of 10 questions. We adapted the instrument to better capture some sources of bias that were not considered in the original 10-item scale.

Question #	Question
1	Do the cases have independent validation?
2	Are the cases representative?
3	Are the controls derived from the community?
4	At the designated endpoint of the study, do the controls have the outcome of interest?
5	Does the study control for the most important confounder?
6	Does the study control for any additional confounders?
7	Was exposure/outcome ascertained through a secure record (surgical, etc.)
8	Was the investigator who assessed exposure/outcome blinded to group patient assignment?
9	Was the same method of exposure/outcome ascertainment used for both groups?
10	Was the nonresponse rate of both groups the same?
11	Was the investigation time of the study the same for both groups?
12	Was the funding free of financial interest?
13	Were the conclusions supported by the data?

Appendix G: Study Summary Tables

See Volume II.

Appendix H: Sensitivity Analyses

Sensitivity Analyses (Key Question 1)

OSA and Crash Rate Ratio

Figure H-1. Removal of One Study at a Time

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Barbe	2.769	1.154	6.646	2.280	0.023
Shiomi	2.755	1.262	6.012	2.544	0.011
Horstmann	1.761	1.279	2.423	3.470	0.001
Lloberes	2.726	1.242	5.981	2.501	0.012
Findley 2000	2.608	1.205	5.644	2.432	0.015
George	3.141	1.503	6.568	3.042	0.002
Stoohs	2.919	1.260	6.761	2.500	0.012
Haraldsson	2.987	1.319	6.769	2.623	0.009
Findley 1988	2.621	1.217	5.644	2.462	0.014
	2.722	1.295	5.722	2.642	0.008

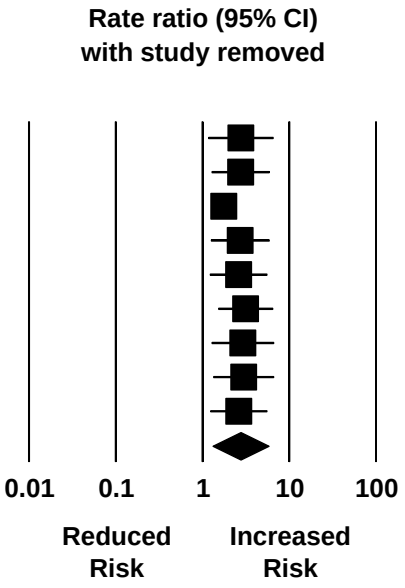


Figure H-2. Cumulative REMA (Highest Weight Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
George	1.306	0.791	2.158	1.043	0.297
Shiomi	1.342	0.822	2.191	1.175	0.240
Horstmann	3.139	0.641	15.372	1.411	0.158
Haraldsson	2.618	0.733	9.351	1.482	0.138
Lloberes	2.636	0.837	8.304	1.656	0.098
Barbe	2.638	1.054	6.606	2.072	0.038
Findley 2000	2.794	1.167	6.689	2.306	0.021
Stoohs	2.621	1.217	5.644	2.462	0.014
Findley 1988	2.722	1.295	5.722	2.642	0.008
	2.722	1.295	5.722	2.642	0.008

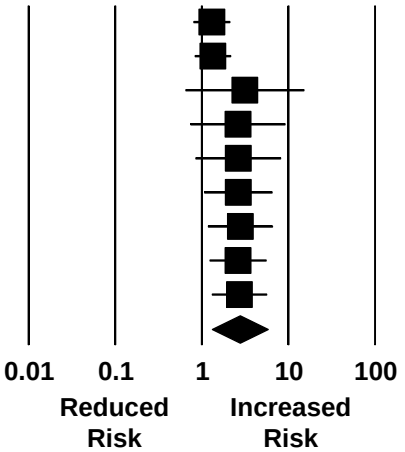


Figure H-3. Cumulative REMA (Most Recent Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Barbe	2.570	1.304	5.065	2.727	0.006
Shiomi	2.551	1.331	4.889	2.821	0.005
Horstmann	4.420	1.544	12.652	2.769	0.006
Lloberes	4.178	1.652	10.566	3.020	0.003
Findley 2000	4.374	1.892	10.113	3.451	0.001
George	3.155	1.178	8.453	2.285	0.022
Stoohs	2.867	1.226	6.704	2.431	0.015
Haraldsson	2.621	1.217	5.644	2.462	0.014
Findley 1988	2.722	1.295	5.722	2.642	0.008
	2.722	1.295	5.722	2.642	0.008

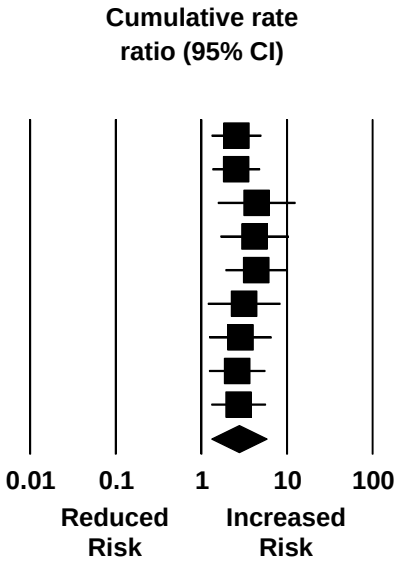


Figure H-4. Cumulative REMA (Oldest Study First)

Study name	Cumulative statistics				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Findley 1988	6.833	0.257	181.694	1.148	0.251
Haraldsson	1.715	0.730	4.028	1.239	0.215
Stoohs	1.788	1.014	3.153	2.008	0.045
George	1.499	1.030	2.184	2.112	0.035
Horstmann	2.646	0.911	7.687	1.788	0.074
Lloberes	2.651	0.993	7.078	1.947	0.052
Findley 2000	2.817	1.111	7.146	2.181	0.029
Shiomi	2.769	1.154	6.646	2.280	0.023
Barbe	2.722	1.295	5.722	2.642	0.008
	2.722	1.295	5.722	2.642	0.008

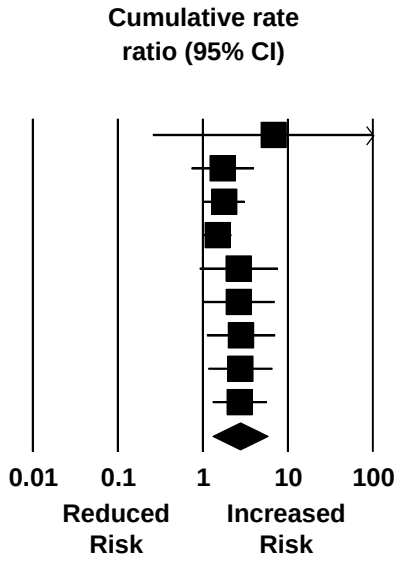
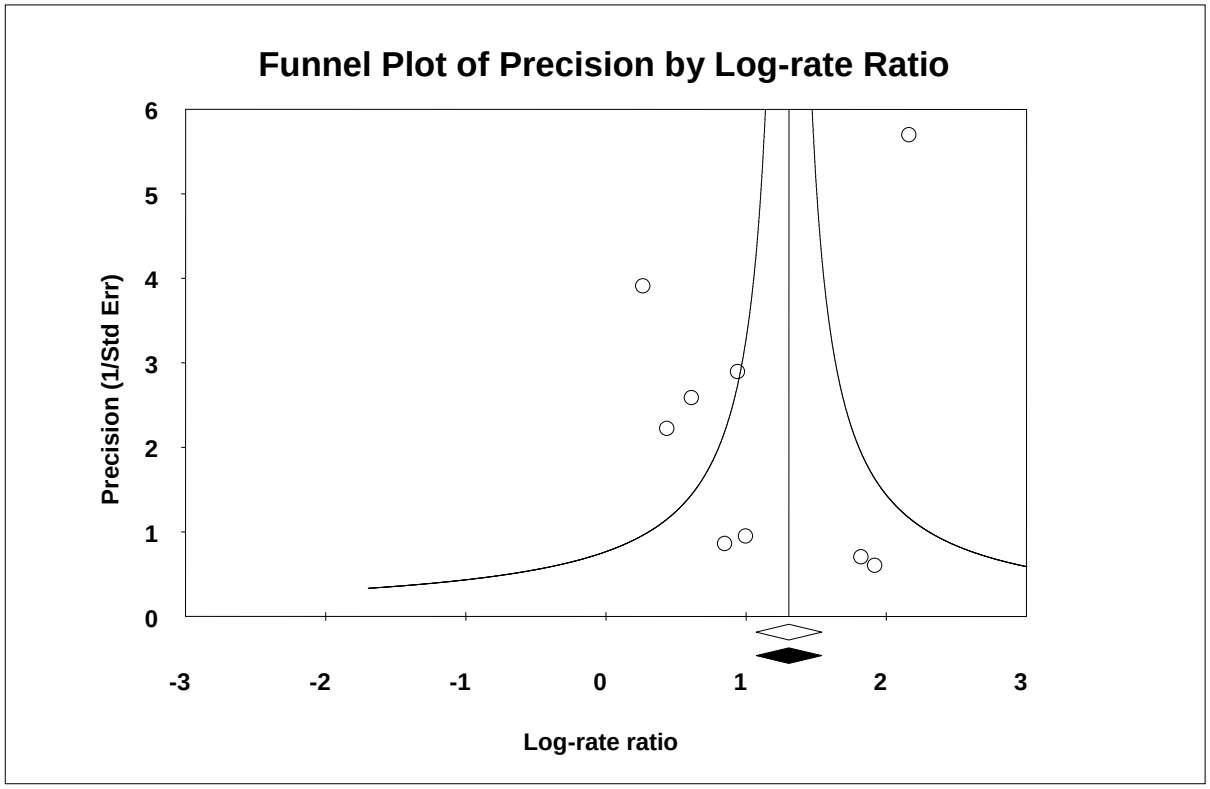


Figure H-5. Publication Bias Test (Trim and Fill)



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		3.69052	2.91993	4.66448	2.72225	1.29513	5.72191	48.86613
Adjusted values	0	3.69052	2.91993	4.66448	2.72225	1.29513	5.72191	48.86613

Sensitivity Analyses (Key Question 5)

Sensitivity Analyses Part A: Reduction in Crash Rate Following Treatment

Figure H-6. Sensitivity Analysis 1: One Study Removed at a Time

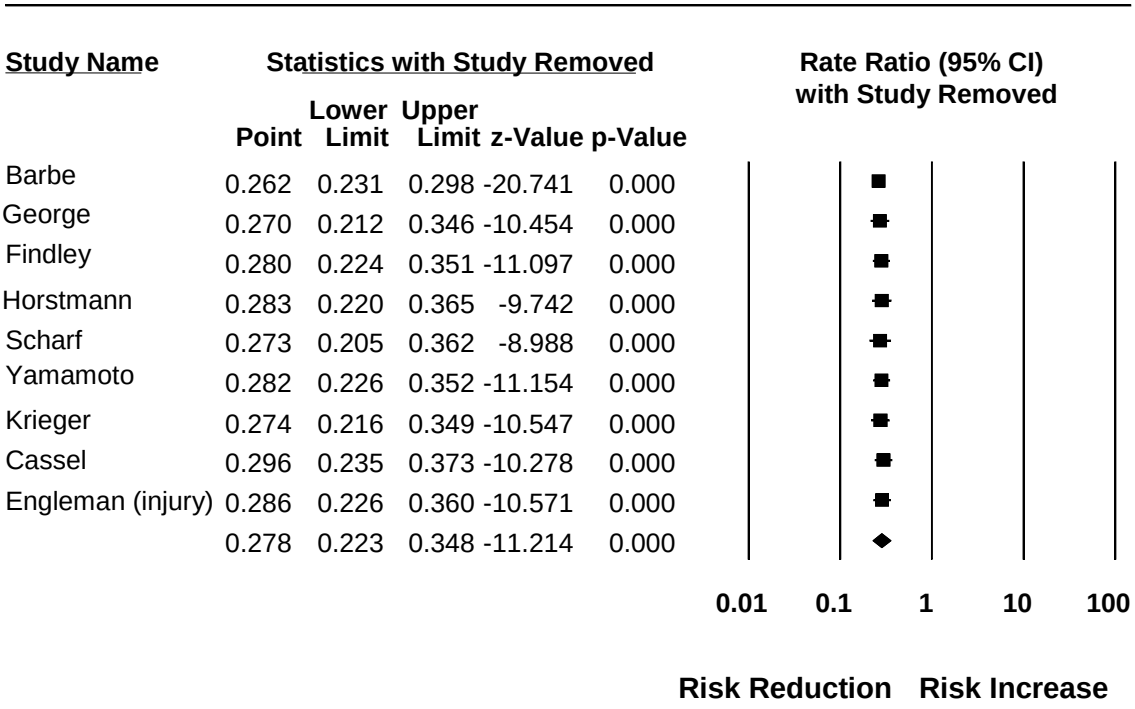


Figure H-7. Sensitivity Analysis 2: Cumulative REMA – Most Recent Study First

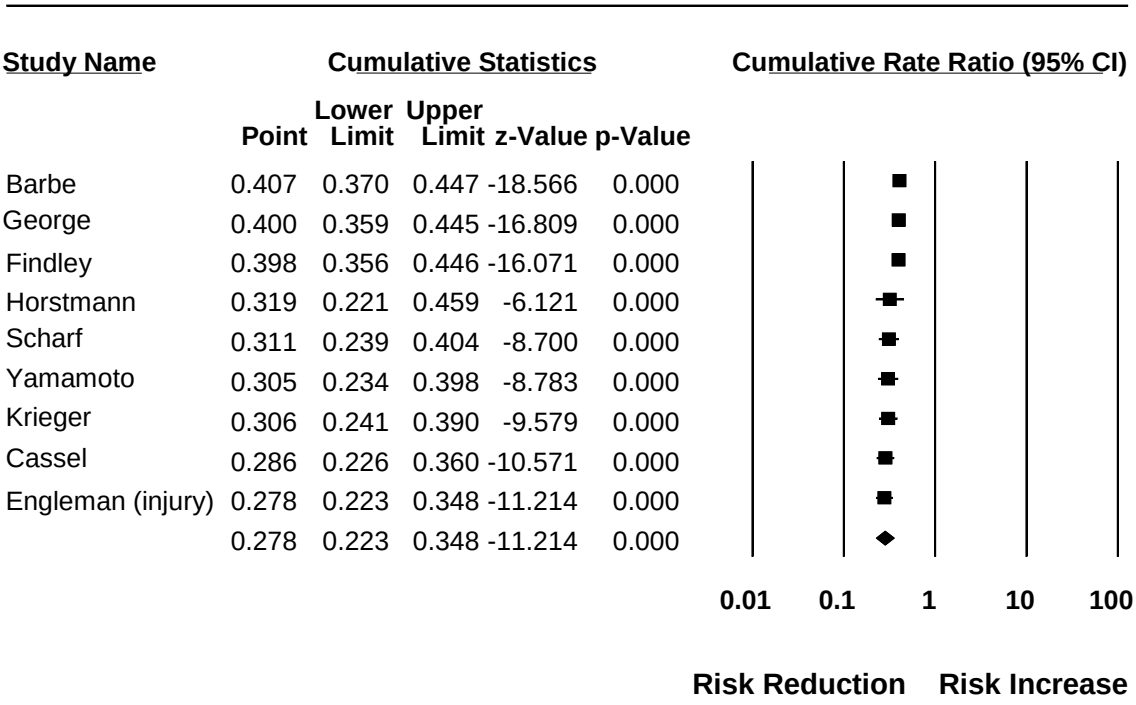


Figure H-8. Sensitivity Analysis 3: Cumulative REMA – Oldest Study First

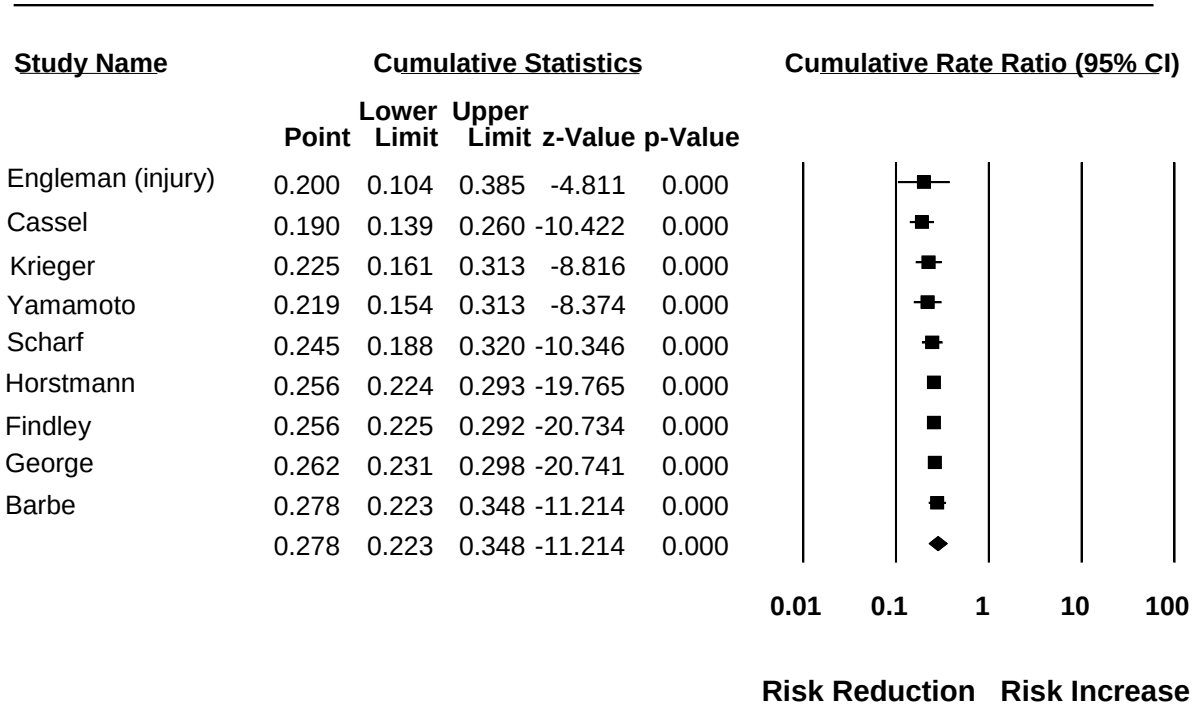


Figure H-9. Sensitivity Analysis 4: Cumulative REMA – Highest Weighted Study First

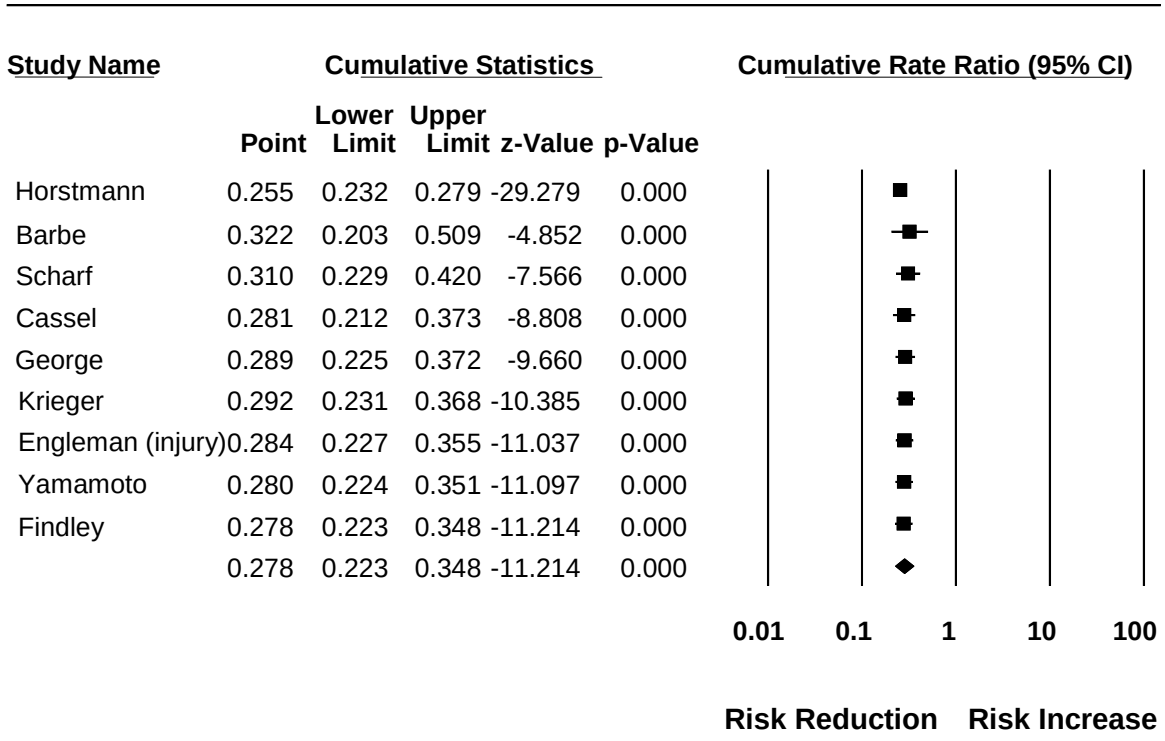
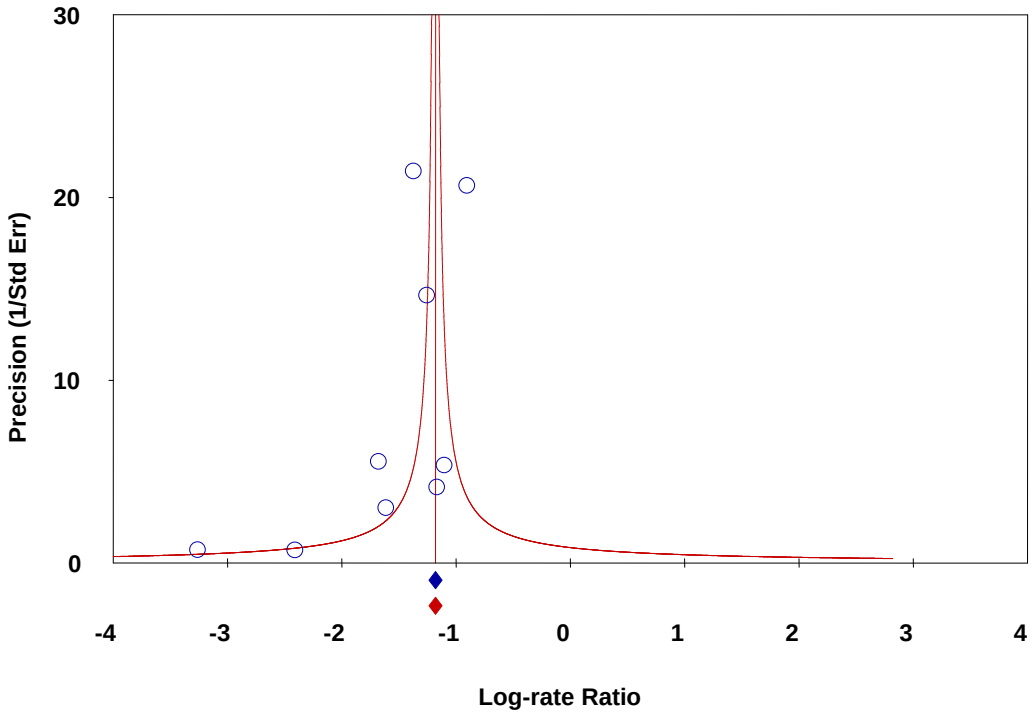


Figure H-10. Sensitivity Analysis 5: Publication Bias Test – Trim and Fill Method



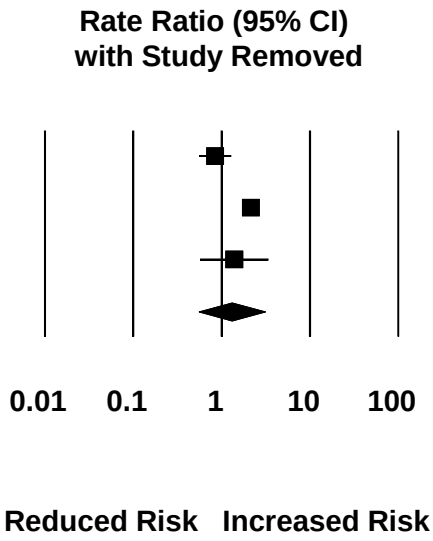
Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.30728	0.29026	0.32530	0.27839	0.22263	0.34811	62.58941
Adjusted values	0	0.30728	0.29026	0.32530	0.27839	0.22263	0.34811	62.58941

Sensitivity Analyses Part B: Crash Rate Following Treatment Compared to Controls

Figure H-11. Sensitivity Analysis 1: One Study Removed at a Time

Study Name	Statistics with Study Removed				
	Point	Lower Limit	Upper Limit	z-Value	p-Value
Barbe	0.846	0.550	1.302	-0.759	0.448
George	2.143	1.859	2.470	10.515	0.000
Findley	1.390	0.565	3.418	0.718	0.473
	1.292	0.546	3.058	0.583	0.560



AHI REMA

Figure H-12. Sensitivity Analysis 2: Cumulative REMA – Most Recent Study First

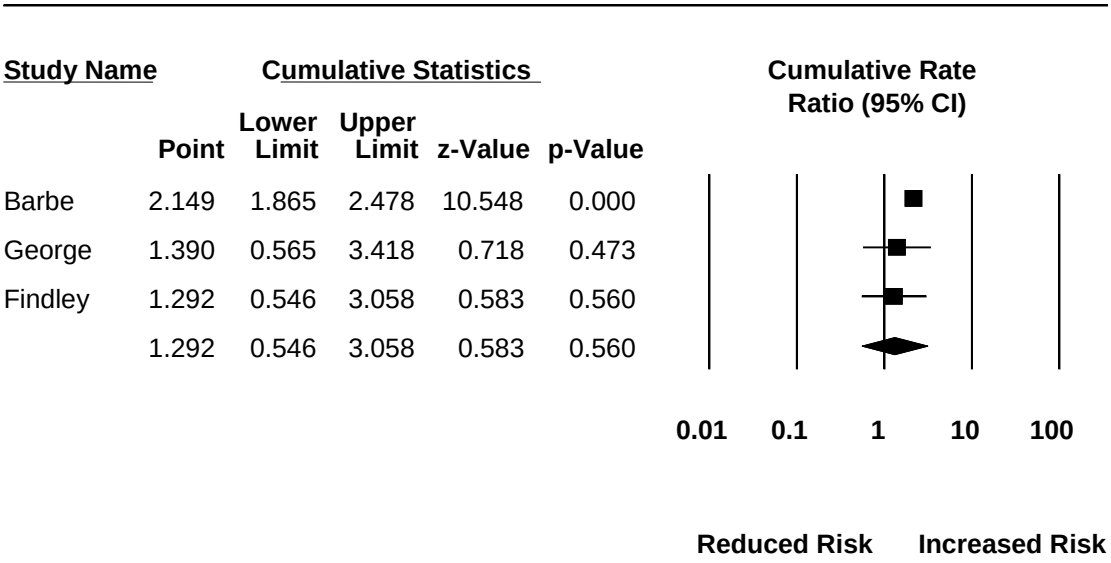
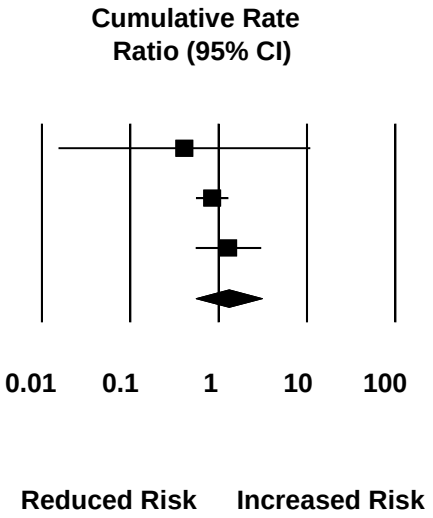


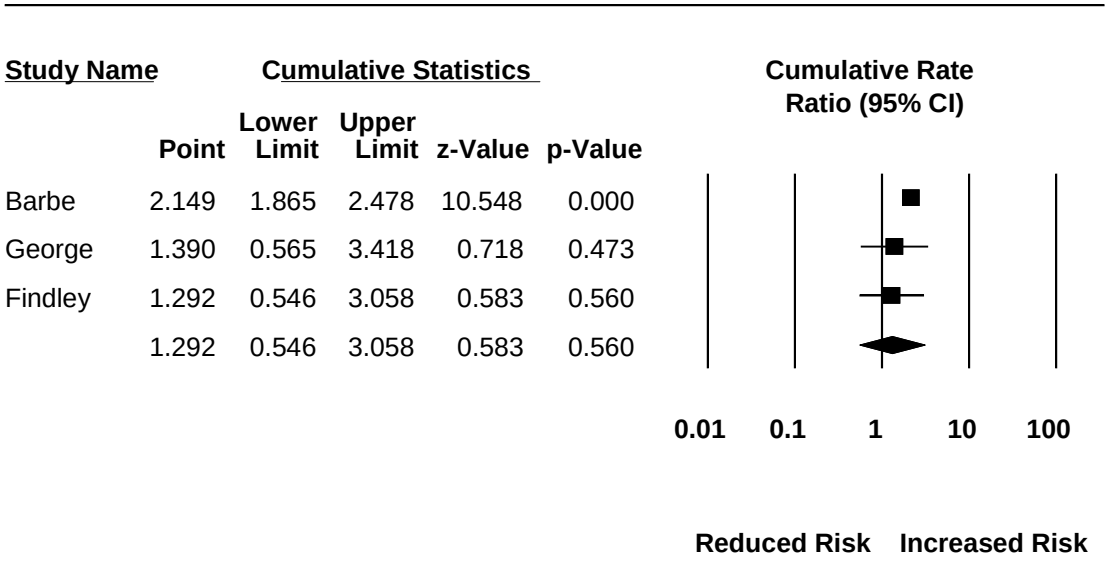
Figure H-13. Sensitivity Analysis 3: Cumulative REMA – Oldest Study First

Study Name	Cumulative Statistics				
	Point	Lower Limit	Upper Limit	z-Value	p-Value
Findley	0.410	0.015	11.014	-0.531	0.595
George	0.846	0.550	1.302	-0.759	0.448
Barbe	1.292	0.546	3.058	0.583	0.560
	1.292	0.546	3.058	0.583	0.560



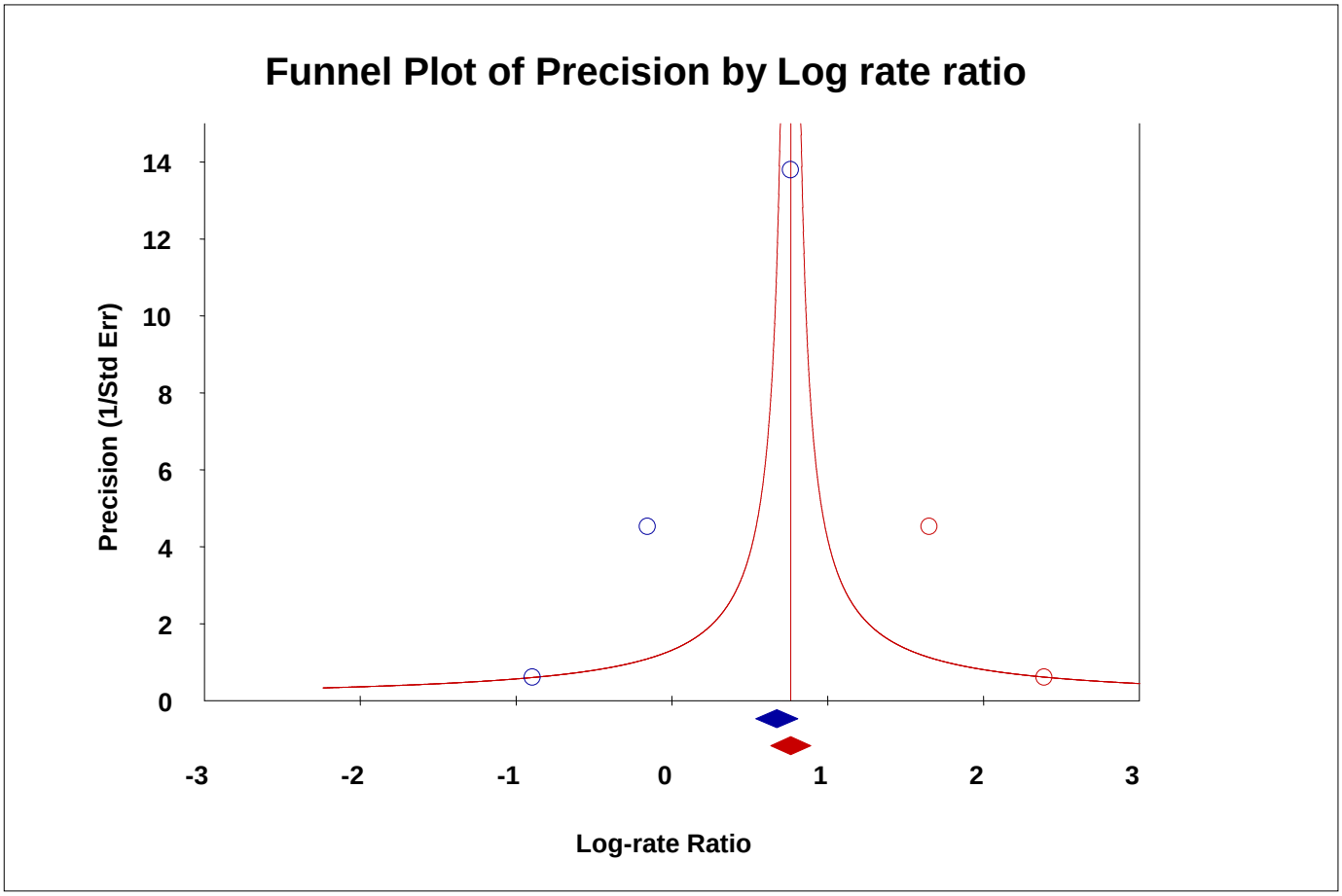
AHI REMA

Figure H-14. Sensitivity Analysis 4: Cumulative REMA – Highest Weighted Study First



AHI REMA

Figure H-15. Sensitivity Analysis 5: Publication Bias – Trim and Fill Method



		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		1.96130	1.71357	2.24483	1.29216	0.54599	3.05809	16.40940
Adjusted values	2	2.14355	1.88442	2.43830	2.12730	1.01567	4.45556	35.19056

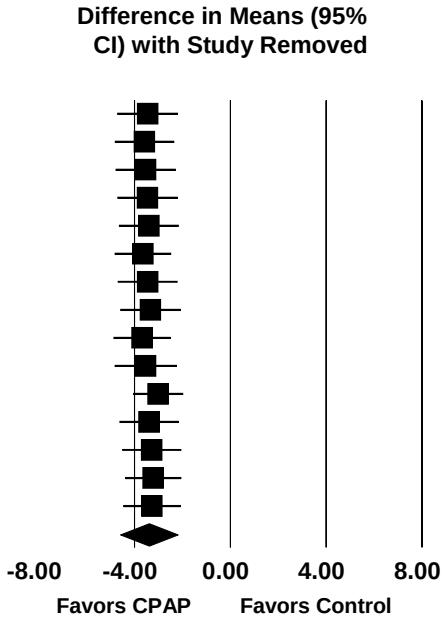
Sensitivity Analyses Part C: Treatment and Indirect Measures of Crash Risk

Daytime Sleepiness

ESS (Parallel arm and first phase of cross-over)

Figure H-16. Sensitivity Analysis 1: REMA – 1 Study Removed at a Time

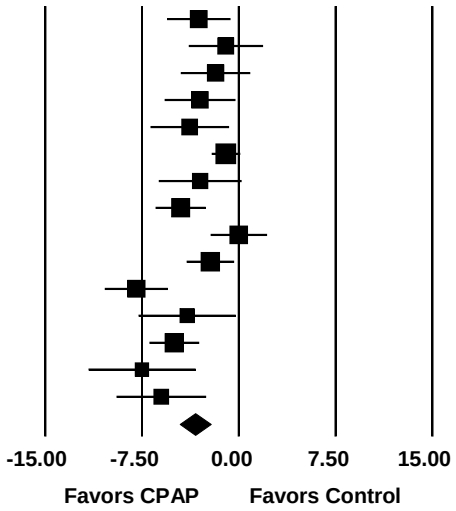
Study Name	Statistics with Study Removed						
	Point	Standard Error	Variance	Lower limit	Upper Limit	z-Value	p-Value
Coughlin	-3.450	0.658	0.433	-4.740	-2.160	-5.241	0.000
Hui	-3.581	0.642	0.412	-4.839	-2.323	-5.579	0.000
Loredo	-3.537	0.651	0.423	-4.812	-2.261	-5.435	0.000
Mansfield	-3.454	0.654	0.427	-4.735	-2.172	-5.283	0.000
Becker	-3.398	0.648	0.419	-4.667	-2.129	-5.247	0.000
Barnes	-3.648	0.612	0.375	-4.848	-2.449	-5.961	0.000
Chakravorty	-3.449	0.648	0.420	-4.718	-2.179	-5.323	0.000
Pepperell	-3.331	0.652	0.425	-4.609	-2.052	-5.107	0.000
Barbe	-3.680	0.620	0.384	-4.896	-2.465	-5.936	0.000
Monasterio	-3.534	0.670	0.450	-4.848	-2.220	-5.271	0.000
Montserrat	-3.014	0.542	0.294	-4.077	-1.952	-5.561	0.000
Henke	-3.390	0.641	0.410	-4.645	-2.134	-5.292	0.000
Ballester	-3.280	0.639	0.408	-4.532	-2.028	-5.134	0.000
Hack	-3.217	0.610	0.372	-4.413	-2.021	-5.271	0.000
Jenkinson	-3.266	0.626	0.392	-4.493	-2.040	-5.220	0.000
	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000



Meta Analysis

Figure H-17. Sensitivity Analysis 2: Cumulative REMA – Newest Study First

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Coughlin	-3.100	1.273	1.619	-5.594	-0.606	-2.436	0.015
Hui	-1.000	1.486	2.209	-3.913	1.913	-0.673	0.501
Loredo	-1.800	1.393	1.939	-4.529	0.929	-1.293	0.196
Mansfield	-3.000	1.418	2.010	-5.778	-0.222	-2.116	0.034
Becker	-3.800	1.570	2.465	-6.877	-0.723	-2.420	0.016
Barnes	-1.000	0.580	0.336	-2.136	0.136	-1.725	0.084
Chakravorty	-3.000	1.654	2.737	-6.242	0.242	-1.813	0.070
Pepperell	-4.500	1.011	1.022	-6.482	-2.518	-4.450	0.000
Barbe	0.000	1.131	1.278	-2.216	2.216	0.000	1.000
Monasterio	-2.200	0.960	0.922	-4.082	-0.318	-2.291	0.022
Montserrat	-7.940	1.264	1.598	-10.418	-5.462	-6.281	0.000
Henke	-4.000	1.940	3.765	-7.803	-0.197	-2.061	0.039
Ballester	-5.000	1.001	1.001	-6.961	-3.039	-4.997	0.000
Hack	-7.500	2.132	4.545	-11.678	-3.322	-3.518	0.000
Jenkinson	-6.000	1.791	3.208	-9.511	-2.489	-3.350	0.001
	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000



Meta Analysis

Figure H-18. Sensitivity Analysis 3: Cumulative REMA – Oldest Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Ballester	-5.000	1.001	1.001	-6.961	-3.039	-4.997	0.000
Hack	-5.541	1.030	1.060	-7.559	-3.523	-5.382	0.000
Jenkinson	-5.563	0.808	0.653	-7.147	-3.979	-6.883	0.000
Henke	-5.332	0.746	0.557	-6.794	-3.870	-7.146	0.000
Barbe	-4.271	1.389	1.928	-6.993	-1.550	-3.076	0.002
Monasterio	-3.801	1.088	1.184	-5.933	-1.668	-3.493	0.000
Montserrat	-4.487	1.146	1.314	-6.733	-2.240	-3.914	0.000
Barnes	-3.958	1.052	1.106	-6.020	-1.897	-3.764	0.000
Chakravorty	-3.844	0.958	0.918	-5.722	-1.966	-4.012	0.000
Pepperell	-3.899	0.862	0.743	-5.589	-2.209	-4.522	0.000
Becker	-3.879	0.800	0.640	-5.447	-2.311	-4.849	0.000
Mansfield	-3.794	0.739	0.547	-5.243	-2.345	-5.131	0.000
Hui	-3.584	0.701	0.492	-4.958	-2.210	-5.112	0.000
Loredo	-3.450	0.658	0.433	-4.740	-2.160	-5.241	0.000
Coughlin	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000
Meta Analysis	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000

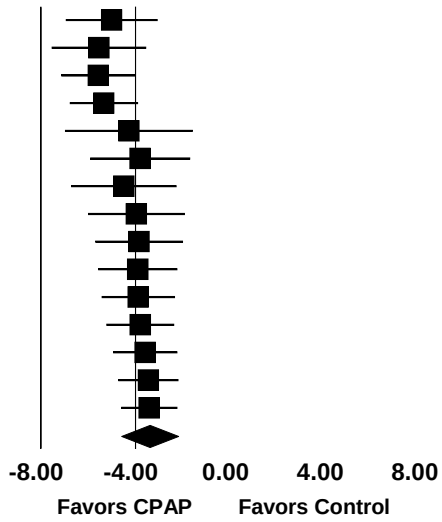


Figure H-19. Sensitivity Analysis 4: Cumulative REMA – Highest Weighted Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barnes	-1.000	0.580	0.336	-2.136	0.136	-1.725	0.084
Monasterio	-1.356	0.548	0.300	-2.430	-0.282	-2.474	0.013
Ballester	-2.636	1.184	1.402	-4.956	-0.315	-2.226	0.026
Pepperell	-3.078	1.029	1.060	-5.095	-1.060	-2.990	0.003
Barbe	-2.513	0.930	0.864	-4.335	-0.691	-2.703	0.007
Montserrat	-3.359	1.094	1.196	-5.503	-1.215	-3.071	0.002
Coughlin	-3.316	0.959	0.920	-5.196	-1.436	-3.457	0.001
Loredo	-3.142	0.866	0.750	-4.838	-1.445	-3.629	0.000
Mansfield	-3.123	0.788	0.622	-4.668	-1.578	-3.961	0.000
Hui	-2.938	0.737	0.543	-4.381	-1.494	-3.989	0.000
Becker	-3.002	0.690	0.477	-4.355	-1.649	-4.348	0.000
Chakravorty	-2.999	0.649	0.421	-4.271	-1.728	-4.625	0.000
Jenkinson	-3.177	0.637	0.406	-4.427	-1.928	-4.985	0.000
Henke	-3.217	0.610	0.372	-4.413	-2.021	-5.271	0.000
Hack	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000
Meta Analysis	-3.415	0.614	0.377	-4.619	-2.212	-5.563	0.000

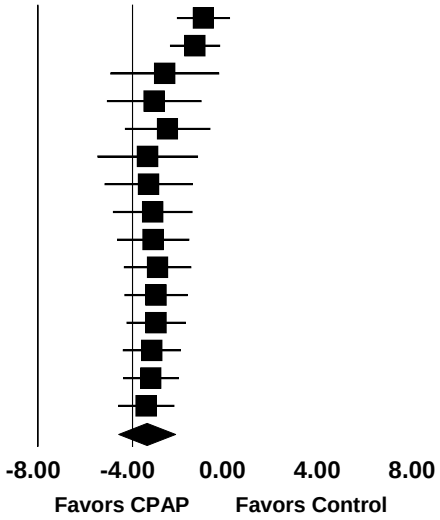
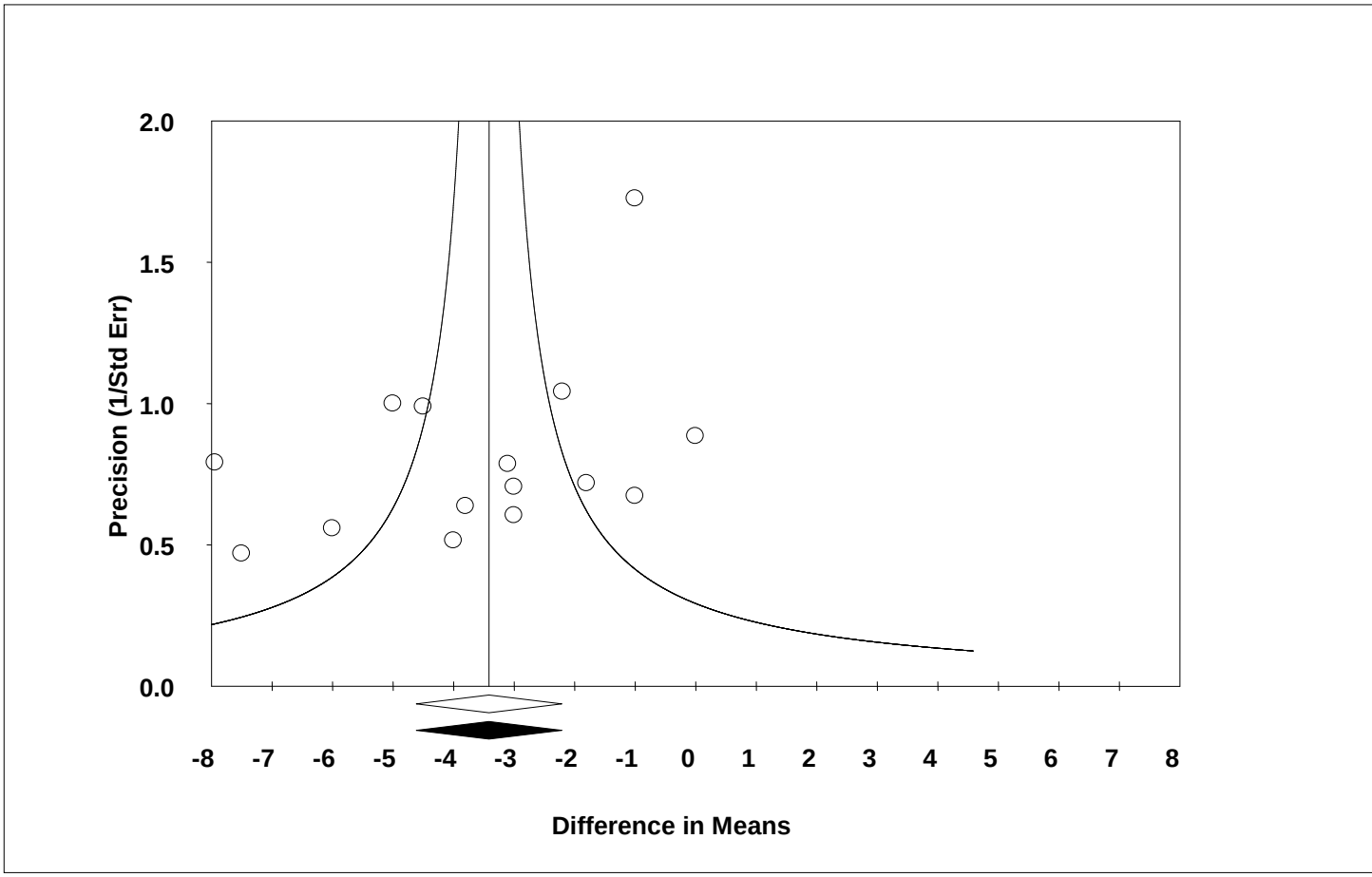


Figure H-20. Sensitivity Analysis 5: Publication Bias Tests (Tweedie and Duval)



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-2.85947	-3.44781	-2.27112	-3.41540	-4.61882	-2.21198	51.23752
Adjusted values	0	-2.85947	-3.44781	-2.27112	-3.41540	-4.61882	-2.21198	51.23752

ESS (Parallel arm- single arm only)

Figure H-21. Sensitivity Analysis 1: REMA – 1 Study Removed at a Time

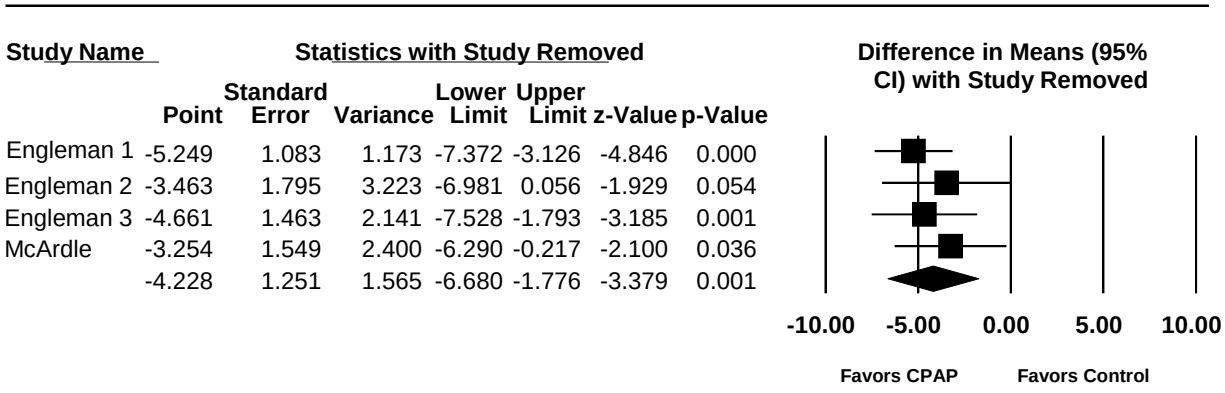


Figure H-22. Sensitivity Analysis 2: Cumulative REMA – Newest Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
McArdle	-6.500	0.514	0.265	-7.508	-5.492	-12.638	0.000
Engleman 3	-4.847	1.747	3.053	-8.271	-1.422	-2.774	0.006
Engleman 2	-5.249	1.083	1.173	-7.372	-3.126	-4.846	0.000
Engleman 1	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001
Meta Analysis	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001

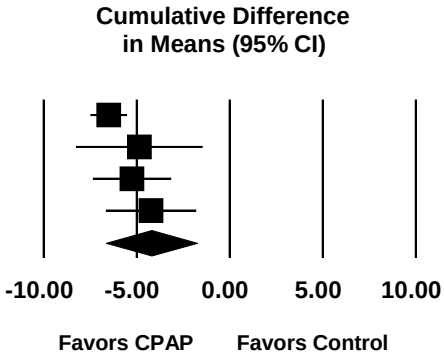
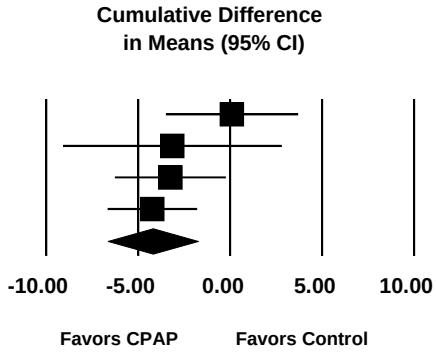


Figure H-23. Sensitivity Analysis 3: Cumulative REMA – Oldest Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Engleman 1	0.100	1.844	3.400	-3.514	3.714	0.054	0.957
Engleman 2	-3.140	3.044	9.267	-9.106	2.827	-1.031	0.302
Engleman 3	-3.254	1.549	2.400	-6.290	-0.217	-2.100	0.036
McArdle	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001
	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001



Meta Analysis

Figure H-24. Sensitivity Analysis 4: Cumulative REMA – Highest Weighted Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
McArdle	-6.500	0.514	0.265	-7.508	-5.492	-12.638	0.000
Engleman 3	-4.847	1.747	3.053	-8.271	-1.422	-2.774	0.006
Engleman 2	-5.249	1.083	1.173	-7.372	-3.126	-4.846	0.000
Engleman 1	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001
Meta Analysis	-4.228	1.251	1.565	-6.680	-1.776	-3.379	0.001

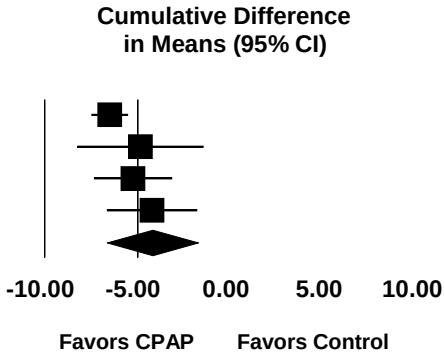
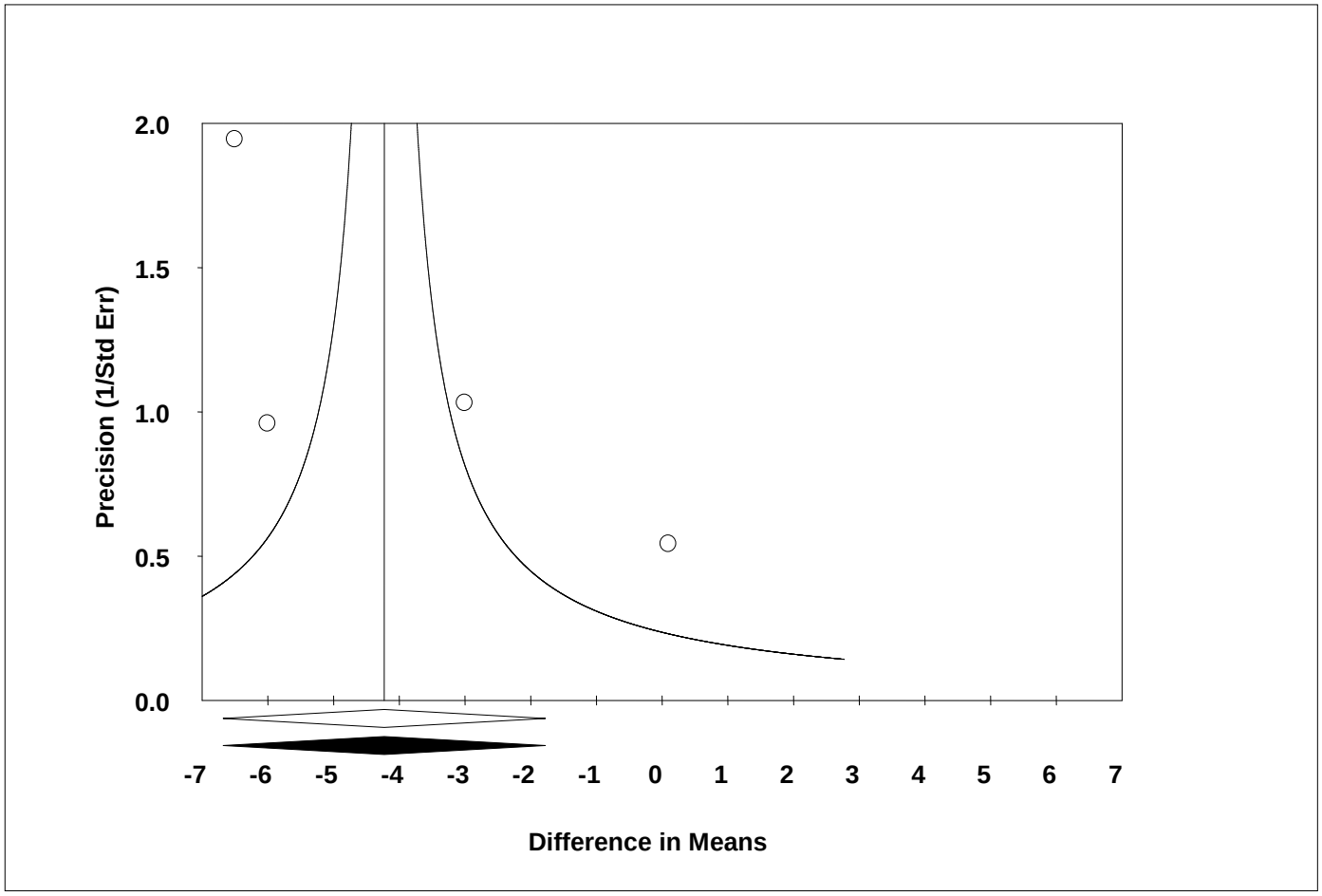


Figure H-25. Sensitivity Analysis 5: Publication Bias Tests (Tweedie and Duval)

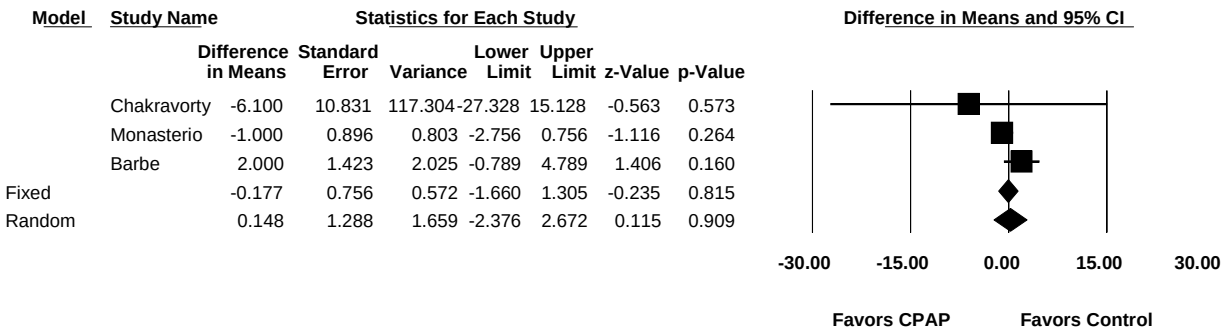


Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-5.48959	-6.28599	-4.69320	-4.22780	-6.68003	-1.77557	19.87378
Adjusted values	0	-5.48959	-6.28599	-4.69320	-4.22780	-6.68003	-1.77557	19.87378

Multiple Sleep Latency Scale (Parallel arm and first phase of cross-over)

Figure H-26. Sensitivity Analysis 1: Difference between FEMA and REMA Estimates



Meta Analysis

Figure H-27. Sensitivity Analysis 2: FEMA – 1 Study Removed at a Time

Study Name	Statistics with Study Removed						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barbe	-1.035	0.893	0.797	-2.784	0.715	-1.159	0.246
Chakravorty	-0.148	0.758	0.575	-1.634	1.337	-0.196	0.845
Monasterio	1.863	1.411	1.990	-0.902	4.628	1.320	0.187
Meta Analysis	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815

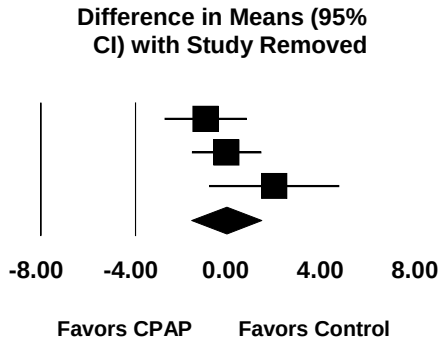
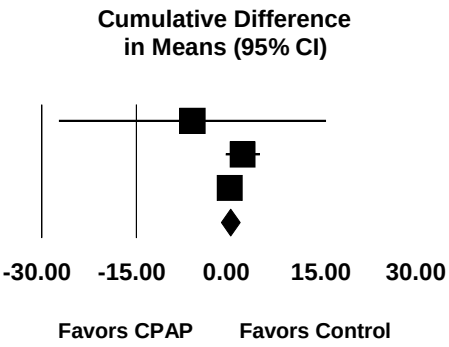


Figure H-28. Sensitivity Analysis 3: Cumulative FEMA – Newest Study First

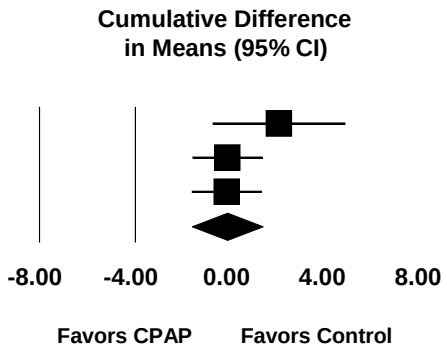
Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Chakravorty	-6.100	10.831	117.304	-27.328	15.128	-0.563	0.573
Barbe	1.863	1.411	1.990	-0.902	4.628	1.320	0.187
Monasterio	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815
	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815



Meta Analysis

Figure H-29. Sensitivity Analysis 4: Cumulative FEMA – Oldest Study First

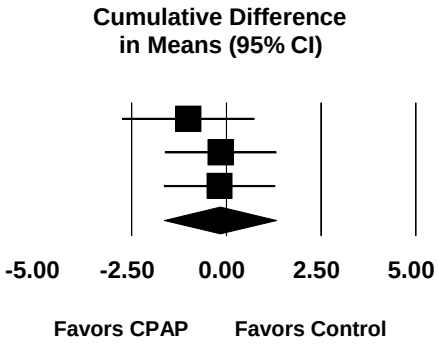
Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barbe	2.000	1.423	2.025	-0.789	4.789	1.406	0.160
Monasterio	-0.148	0.758	0.575	-1.634	1.337	-0.196	0.845
Chakravorty	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815
	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815



Meta Analysis

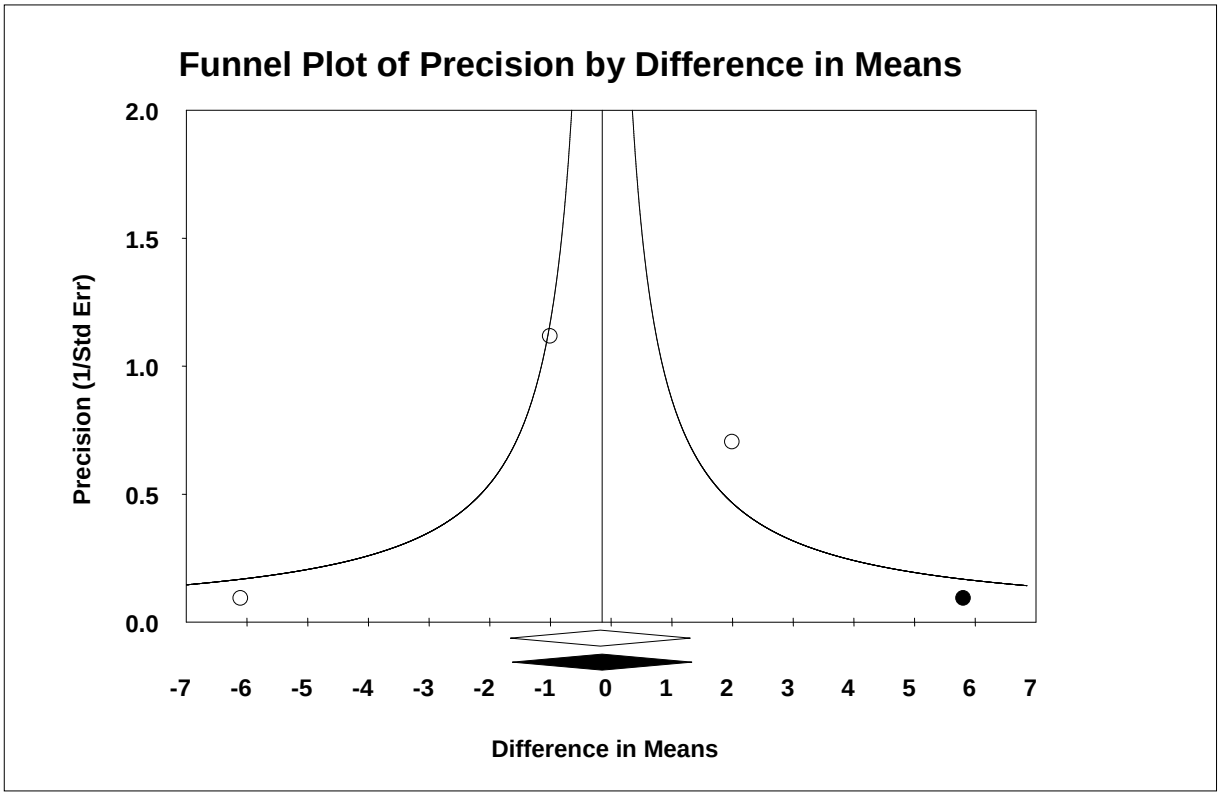
Figure H-30. Sensitivity Analysis 5: Cumulative FEMA – Highest Weighted Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Monasterio	-1.000	0.896	0.803	-2.756	0.756	-1.116	0.264
Barbe	-0.148	0.758	0.575	-1.634	1.337	-0.196	0.845
Chakravorty	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815
	-0.177	0.756	0.572	-1.660	1.305	-0.235	0.815



Meta Analysis

Figure H-31. Sensitivity Analysis 6: Publication Bias Tests (Tweedie and Duval)



Duval and Tweedie's trim and fill

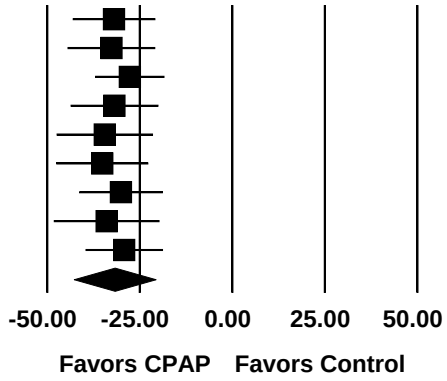
		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-0.17742	-1.65966	1.30482	0.14796	-2.37641	2.67232	3.48397
Adjusted values	1	-0.14837	-1.62702	1.33027	0.12603	-1.97178	2.22384	3.78801

Severity of OSA

AHI (Parallel arm and first phase of crossover)

Figure H-32. Sensitivity Analysis 2: REMA – 1 Study Removed at a Time

Study Name	Statistics with Study Removed						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Becker	-31.959	5.749	33.046	-43.226	-20.692	-5.559	0.000
Chakravorty	-32.658	6.102	37.236	-44.618	-20.698	-5.352	0.000
Henke	-27.686	4.854	23.562	-37.200	-18.173	-5.704	0.000
Kaneko	-31.840	6.109	37.325	-43.814	-19.865	-5.212	0.000
Mansfield	-34.444	6.711	45.039	-47.597	-21.290	-5.132	0.000
Monasterio	-35.122	6.393	40.873	-47.653	-22.592	-5.494	0.000
Norman	-30.082	5.836	34.062	-41.521	-18.643	-5.154	0.000
Pepperell	-33.919	7.343	53.914	-48.310	-19.527	-4.619	0.000
Ryan	-29.179	5.400	29.164	-39.764	-18.595	-5.403	0.000
	-31.897	5.642	31.835	-42.956	-20.839	-5.653	0.000



Meta Analysis

Figure H-33. Sensitivity Analysis 3: Cumulative REMA – Newest Study First

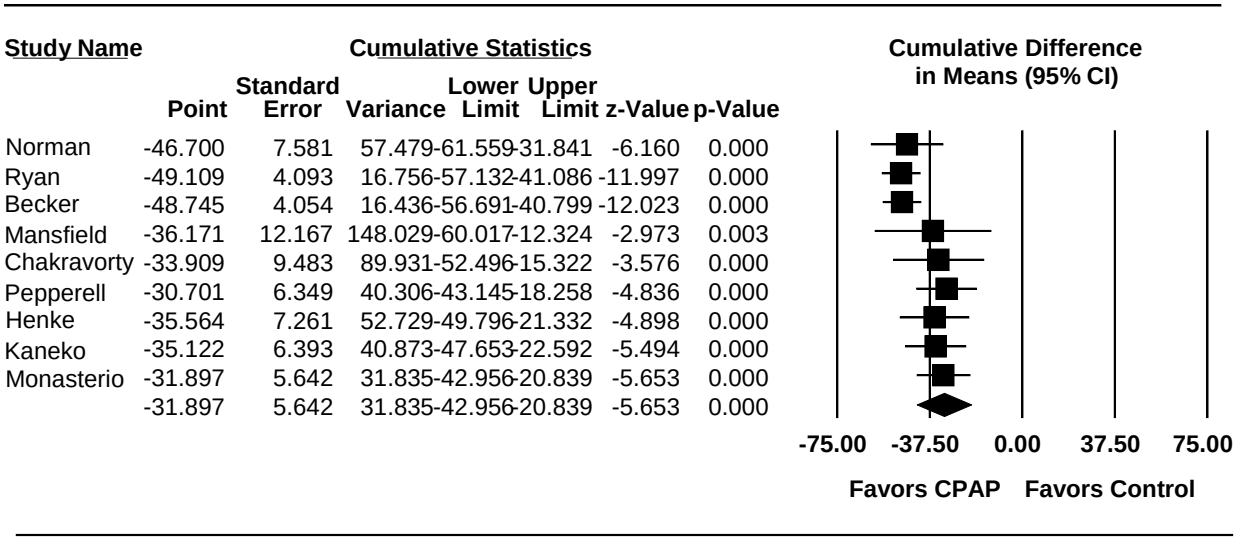


Figure H-34. Sensitivity Analysis 4: Cumulative REMA – Oldest Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Henke	-59.800	5.223	27.280	-70.037	-49.563	-11.449	0.000
Kaneko	-46.234	13.650	186.316	-72.987	-19.481	-3.387	0.001
Monasterio	-34.171	15.663	245.318	-64.870	-3.473	-2.182	0.029
Chakravorty	-32.155	12.211	149.106	-56.088	-8.222	-2.633	0.008
Pepperell	-29.233	7.096	50.350	-43.141	-15.326	-4.120	0.000
Becker	-29.260	6.895	47.545	-42.774	-15.745	-4.243	0.000
Mansfield	-26.715	5.496	30.205	-37.487	-15.943	-4.861	0.000
Ryan	-30.082	5.836	34.062	-41.521	-18.643	-5.154	0.000
Norman	-31.897	5.642	31.835	-42.956	-20.839	-5.653	0.000
Meta Analysis	-31.897	5.642	31.835	-42.956	-20.839	-5.653	0.000

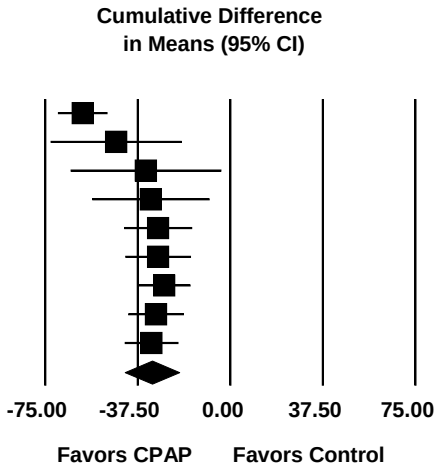
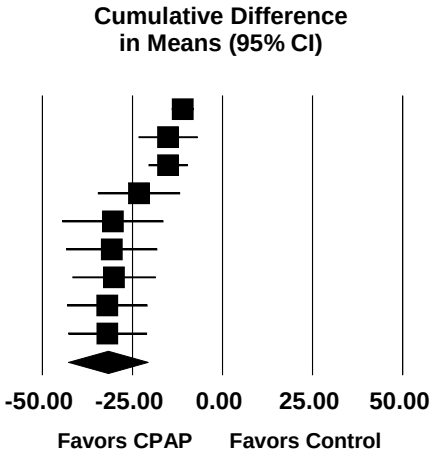


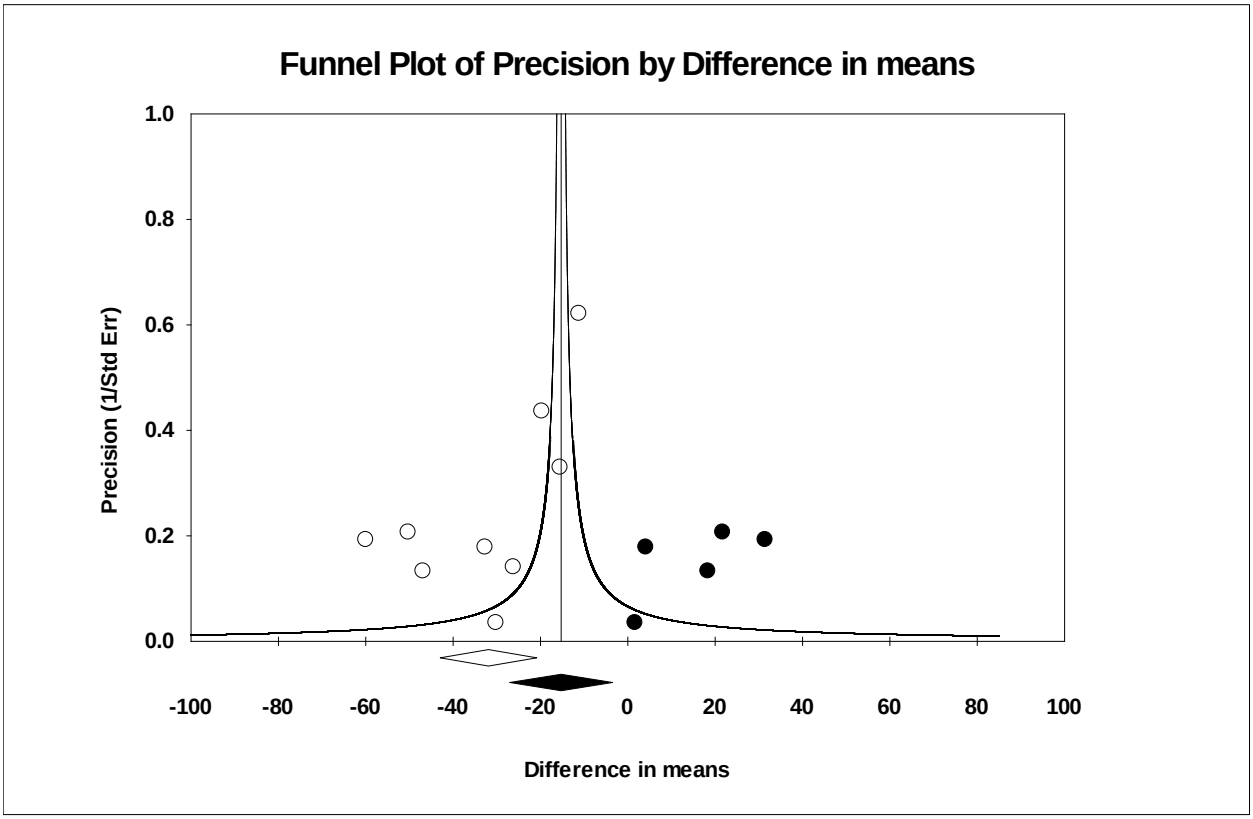
Figure H-35. Sensitivity Analysis 5: Cumulative REMA – Highest Weighted Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Monasterio	-11.000	1.612	2.599	-14.160	-7.840	-6.823	0.000
Pepperell	-15.092	4.247	18.038	-23.416	-6.768	-3.554	0.000
Mansfield	-15.084	2.832	8.019	-20.635	-9.534	-5.327	0.000
Ryan	-23.157	5.883	34.607	-34.687	-11.627	-3.936	0.000
Henke	-30.407	7.219	52.117	-44.557	-16.258	-4.212	0.000
Kaneko	-30.714	6.512	42.407	-43.477	-17.951	-4.717	0.000
Chakravorty	-30.090	5.955	35.467	-41.762	-18.417	-5.052	0.000
Norman	-31.959	5.749	33.046	-43.226	-20.692	-5.559	0.000
Becker	-31.897	5.642	31.835	-42.956	-20.839	-5.653	0.000
	-31.897	5.642	31.835	-42.956	-20.839	-5.653	0.000



Meta Analysis

Figure H-36. Sensitivity Analysis 6: Publication Bias Tests (Tweedie and Duval)



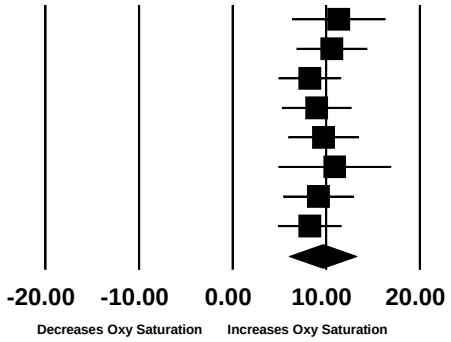
Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-19.58219	-21.73312	-17.43127	-31.89719	-42.95595	-20.83842	147.95084
Adjusted values	0	-19.58219	-21.73312	-17.43127	-31.89719	-42.95595	-20.83842	147.95084

SaO_2 (Parallel arm and first phase of crossover)

Figure H-37. Sensitivity Analysis 2: REMA – 1 Study Removed at a Time

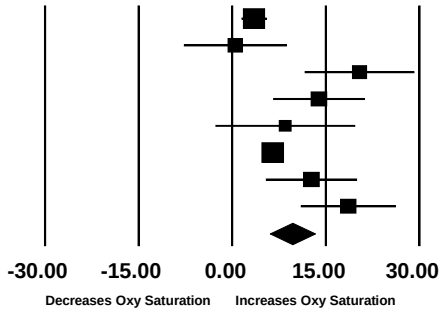
Study Name	Statistics with Study Removed						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Norman	11.346	2.574	6.626	6.301	16.391	4.408	0.000
Hui	10.604	1.955	3.821	6.773	14.435	5.425	0.000
Ryan	8.249	1.734	3.006	4.851	11.647	4.757	0.000
Mansfield	8.991	1.923	3.697	5.222	12.760	4.676	0.000
Becker	9.711	1.951	3.805	5.888	13.534	4.979	0.000
Barnes	10.917	3.096	9.586	4.848	16.985	3.526	0.000
Kaneko	9.178	1.954	3.816	5.349	13.007	4.698	0.000
Henke	8.243	1.754	3.076	4.806	11.680	4.700	0.000
	9.582	1.846	3.406	5.964	13.199	5.192	0.000



Meta Analysis

Figure H-38. Sensitivity Analysis 3: Cumulative REMA – Newest Study First

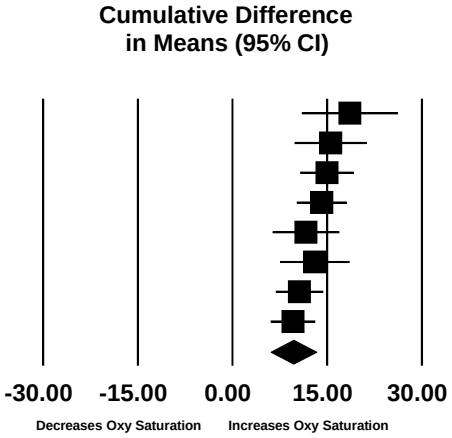
Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Norman	3.500	1.068	1.141	1.407	5.593	3.277	0.001
Hui	3.322	1.036	1.073	1.292	5.352	3.207	0.001
Ryan	7.646	4.995	24.952	-2.144	17.436	1.531	0.126
Mansfield	9.131	4.128	17.038	1.041	17.222	2.212	0.027
Becker	8.967	3.515	12.358	2.076	15.857	2.551	0.011
Barnes	7.602	1.837	3.373	4.002	11.201	4.139	0.000
Kaneko	8.243	1.754	3.076	4.806	11.680	4.700	0.000
Henke	9.582	1.846	3.406	5.964	13.199	5.192	0.000
	9.582	1.846	3.406	5.964	13.199	5.192	0.000



Meta Analysis

Figure H-39. Sensitivity Analysis 4: Cumulative REMA – Oldest Study First

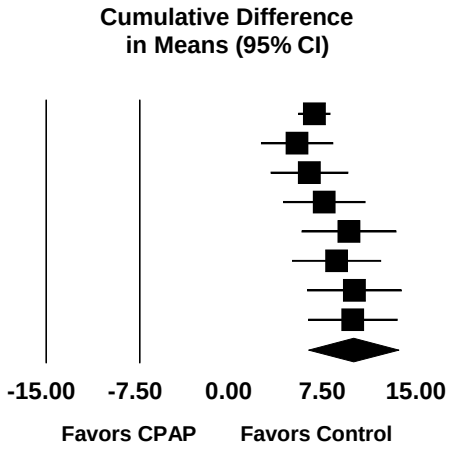
Study Name	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Henke	18.600	3.927	15.419	10.904	26.296	4.737	0.000
Kaneko	15.544	2.948	8.691	9.766	21.322	5.273	0.000
Mansfield	14.972	2.207	4.870	10.647	19.297	6.785	0.000
Becker	14.141	2.060	4.244	10.103	18.179	6.864	0.000
Barnes	11.636	2.730	7.452	6.285	16.986	4.262	0.000
Ryan	13.051	2.848	8.109	7.469	18.632	4.583	0.000
Norman	10.604	1.955	3.821	6.773	14.435	5.425	0.000
Hui	9.582	1.846	3.406	5.964	13.199	5.192	0.000
	9.582	1.846	3.406	5.964	13.199	5.192	0.000



Meta Analysis

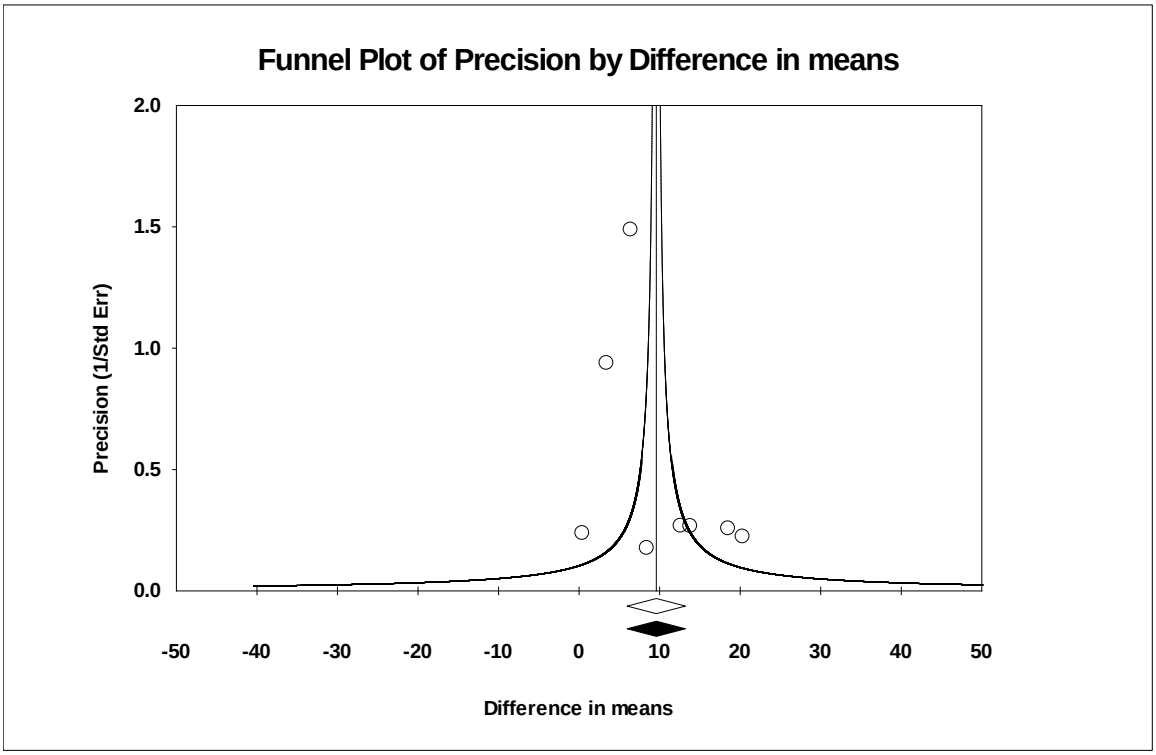
Figure H-40. Sensitivity Analysis 5: Cumulative REMA – Highest Weighted Study First

Study Name	Cumulative Statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barnes	6.500	0.673	0.453	5.181	7.819	9.657	0.000
Norman	5.115	1.496	2.237	2.183	8.046	3.420	0.001
Kaneko	6.103	1.607	2.584	2.952	9.253	3.796	0.000
Mansfield	7.295	1.703	2.900	3.957	10.633	4.284	0.000
Henke	9.269	1.959	3.838	5.429	13.108	4.731	0.000
Hui	8.283	1.839	3.381	4.679	11.887	4.504	0.000
Ryan	9.711	1.951	3.805	5.888	13.534	4.979	0.000
Becker	9.582	1.846	3.406	5.964	13.199	5.192	0.000
	9.582	1.846	3.406	5.964	13.199	5.192	0.000



Meta Analysis

Figure H-41. Sensitivity Analysis 6: Publication Bias Tests (Tweedie and Duval)



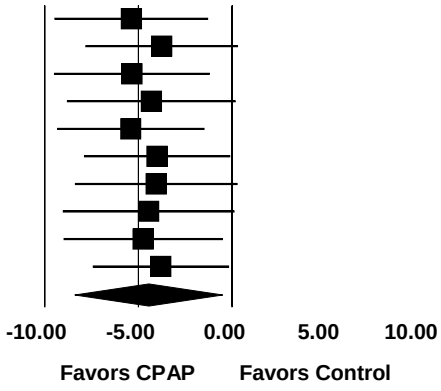
Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		6.35948	5.30020	7.41875	9.58164	5.96422	13.19905	35.42373
Adjusted values	0	6.35948	5.30020	7.41875	9.58164	5.96422	13.19905	35.42373

24-Hour Systolic Blood Pressure (Parallel arm and first phase of crossover)

Figure H-42. Sensitivity Analysis 2: REMA – 1 Study Removed at a Time

Study Name	Statistics with Study Removed						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barbe	-5.369	2.109	4.446	-9.502	-1.236	-2.546	0.011
Becker	-3.747	2.092	4.378	-7.848	0.354	-1.791	0.073
Campos-Rodriguez	-5.339	2.136	4.563	-9.526	-1.152	-2.499	0.012
Coughlin	-4.299	2.314	5.353	-8.833	0.236	-1.858	0.063
Hui	-5.395	2.016	4.065	-9.346	-1.443	-2.676	0.007
Kaneko	-3.993	2.004	4.018	-7.921	-0.064	-1.992	0.046
Monasterio	-4.041	2.230	4.972	-8.411	0.330	-1.812	0.070
Pepperell	-4.448	2.353	5.537	-9.060	0.164	-1.890	0.059
Robinson	-4.732	2.182	4.759	-9.008	-0.456	-2.169	0.030
Usui	-3.791	1.866	3.484	-7.450	-0.133	-2.031	0.042
	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026



Meta Analysis

Figure H-43. Sensitivity Analysis 3: Cumulative REMA – Newest Study First

Study Name	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Coughlin	-6.500	3.124	9.759	-12.623	-0.377	-2.081	0.037
Robinson	-5.604	2.771	7.676	-11.034	-0.173	-2.023	0.043
Hui	-2.038	3.467	12.021	-8.834	4.758	-0.588	0.557
Campos-Rodriguez	-1.107	2.569	6.598	-6.141	3.927	-0.431	0.666
Usui	-2.772	3.283	10.781	-9.207	3.664	-0.844	0.399
Kaneko	-4.112	3.306	10.933	-10.592	2.369	-1.244	0.214
Becker	-5.238	3.017	9.103	-11.151	0.675	-1.736	0.083
Pepperell	-5.040	2.419	5.852	-9.781	-0.298	-2.083	0.037
Monasterio	-5.369	2.109	4.446	-9.502	-1.236	-2.546	0.011
Barbe	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026
Meta Analysis	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026

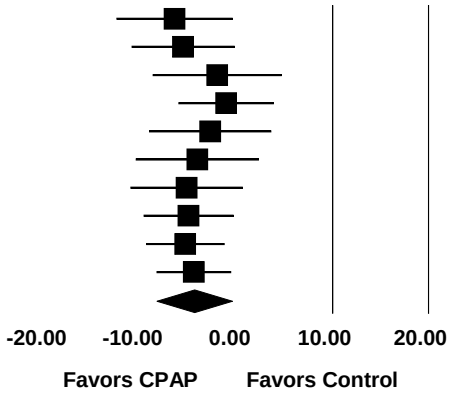
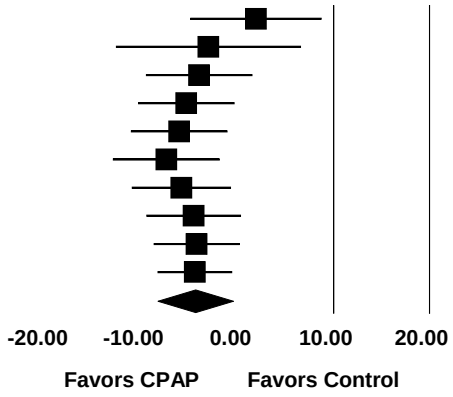


Figure H-44. Sensitivity Analysis 4: Cumulative REMA – Oldest Study First

Study Name	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Barbe	1.900	3.519	12.387	-4.998	8.798	0.540	0.589
Monasterio	-3.065	4.950	24.502	-12.767	6.637	-0.619	0.536
Pepperell	-4.035	2.859	8.172	-9.638	1.568	-1.412	0.158
Becker	-5.371	2.594	6.727	-10.455	-0.287	-2.071	0.038
Kaneko	-6.120	2.596	6.741	-11.209	-1.031	-2.357	0.018
Usui	-7.451	2.870	8.238	-13.077	-1.826	-2.596	0.009
Campos-Rodriguez	-5.888	2.666	7.105	-11.112	-0.663	-2.209	0.027
Hui	-4.610	2.546	6.482	-9.600	0.380	-1.811	0.070
Robinson	-4.299	2.314	5.353	-8.833	0.236	-1.858	0.063
Coughlin	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026
	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026

Cumulative Statistics

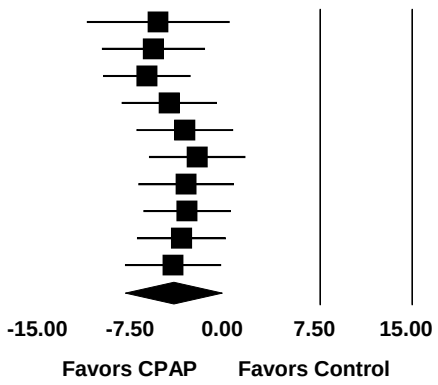
Cumulative Difference in Means (95% CI)



Meta Analysis

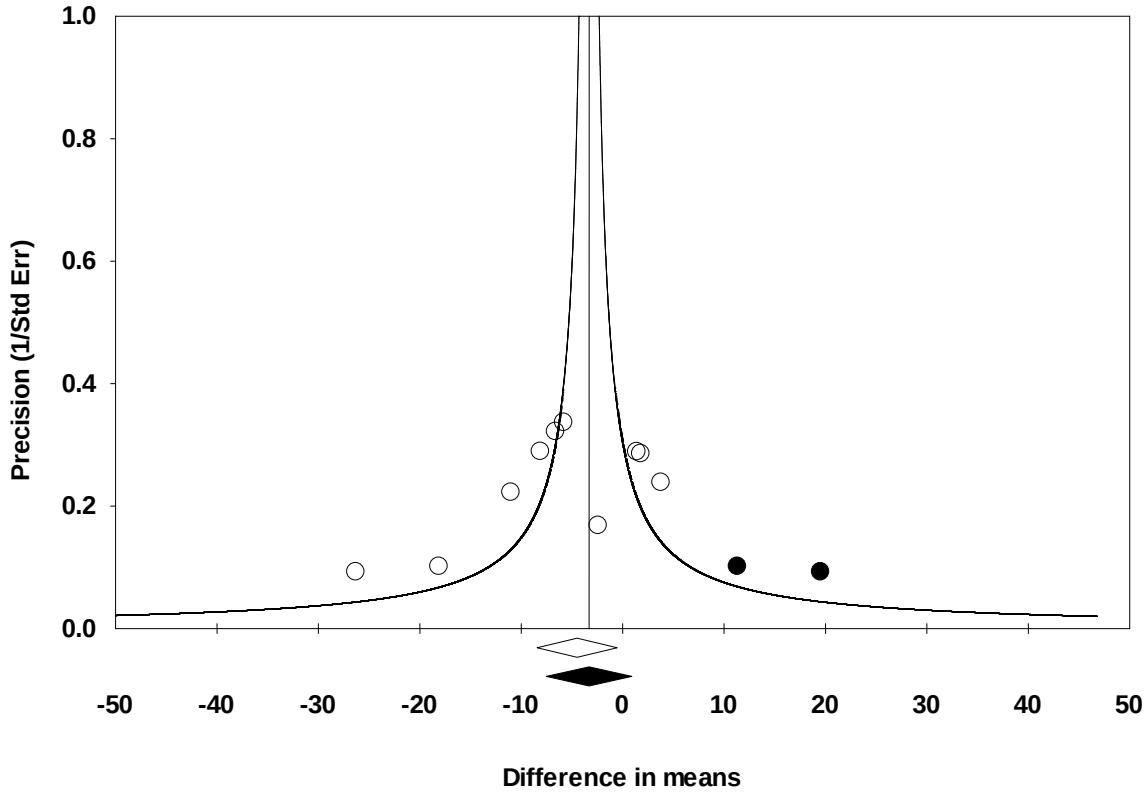
Figure H-45. Sensitivity Analysis 5: Cumulative REMA – Highest Weighted Study First

Study Name	Cumulative statistics						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Pepperell	-5.700	2.983	8.900	-11.547	0.147	-1.911	0.056
Coughlin	-6.082	2.157	4.655	-10.310	-1.853	-2.819	0.005
Monasterio	-6.615	1.833	3.360	-10.208	-3.022	-3.609	0.000
Campos-Rodriguez	-4.795	1.994	3.978	-8.704	-0.886	-2.404	0.016
Barbe	-3.523	2.030	4.122	-7.502	0.457	-1.735	0.083
Hui	-2.507	2.023	4.093	-6.472	1.458	-1.239	0.215
Becker	-3.422	2.004	4.016	-7.350	0.505	-1.708	0.088
Robinson	-3.351	1.833	3.359	-6.944	0.241	-1.828	0.067
Kaneko	-3.791	1.866	3.484	-7.450	-0.133	-2.031	0.042
Usui	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026
	-4.485	2.014	4.056	-8.432	-0.538	-2.227	0.026



Meta Analysis

Figure H-46. Sensitivity Analysis 6: Publication Bias Tests (Tweedie and Duval)



Duval and Tweedie's trim and fill

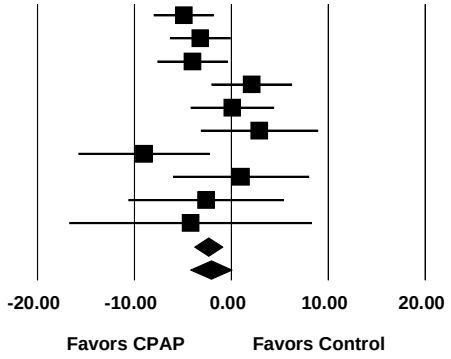
		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-4.02889	-6.53435	-1.52343	-4.48488	-8.43201	-0.53775	19.55928
Adjusted values	2	-3.47204	-5.94086	-1.00322	-3.30958	-7.53017	0.91100	26.39977

Some evidence of publication bias – Adjustment for missing studies does not overturn overall findings

Diastolic Blood Pressure (Parallel arm and first phase of crossover)

Figure H-47. Sensitivity Analysis 1: Difference between FEMA and REMA Estimates

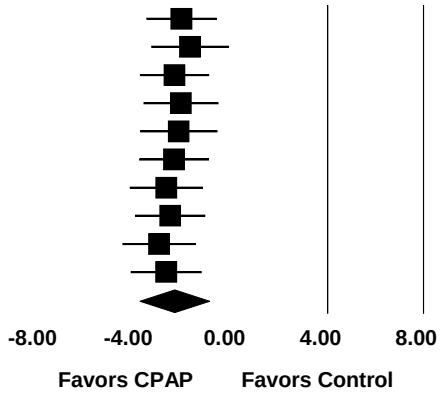
Model	Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
	Coughlin	-4.900	1.607	2.582	-8.049	-1.751	-3.049	0.002
	Pepperell	-3.200	1.628	2.651	-6.391	-0.009	-1.965	0.049
	Monasterio	-4.000	1.878	3.528	-7.681	-0.319	-2.130	0.033
	Barbe	2.100	2.145	4.601	-2.104	6.304	0.979	0.328
	Campos-Rodriguez	0.100	2.219	4.926	-4.250	4.450	0.045	0.964
	Hui	2.900	3.111	9.678	-3.197	8.997	0.932	0.351
	Becker	-9.000	3.474	12.066	-15.808	-2.192	-2.591	0.010
	Kaneko	1.000	3.605	12.999	-6.067	8.067	0.277	0.782
	Robinson	-2.600	4.119	16.966	-10.673	5.473	-0.631	0.528
	Usui	-4.200	6.408	41.061	-16.759	8.359	-0.655	0.512
Fixed		-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001
Random		-2.146	1.088	1.184	-4.279	-0.013	-1.972	0.049



Meta Analysis

Figure H-48. Sensitivity Analysis 2: FEMA – 1 Study Removed at a Time

Study Name	Statistics with Study Removed						
	Point	Standard Error	Variance	Lower Limit	Upper Limit	Z-Value	p-Value
Becker	-2.102	0.760	0.577	-3.592	-0.613	-2.767	0.006
Coughlin	-1.744	0.837	0.701	-3.384	-0.103	-2.083	0.037
Usui	-2.393	0.747	0.559	-3.858	-0.928	-3.202	0.001
Monasterio	-2.124	0.808	0.653	-3.708	-0.540	-2.629	0.009
Pepperell	-2.212	0.834	0.696	-3.847	-0.577	-2.652	0.008
Robinson	-2.411	0.755	0.570	-3.890	-0.932	-3.195	0.001
Campos-Rodriguez	-2.734	0.788	0.620	-4.278	-1.190	-3.471	0.001
Kaneko	-2.569	0.759	0.575	-4.055	-1.082	-3.386	0.001
Barbe	-3.032	0.791	0.626	-4.583	-1.481	-3.832	0.000
Hui	-2.738	0.764	0.584	-4.236	-1.240	-3.582	0.000
	-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001



Meta Analysis

Figure H-49. Sensitivity Analysis 3: Cumulative FEMA – Newest Study First

Study Name	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Coughlin	-4.900	1.607	2.582	-8.049	-1.751	-3.049	0.002
Robinson	-4.596	1.497	2.241	-7.530	-1.662	-3.070	0.002
Campos-Rodriguez	-3.128	1.241	1.540	-5.560	-0.695	-2.520	0.012
Hui	-2.300	1.153	1.329	-4.560	-0.041	-1.995	0.046
Usui	-2.360	1.135	1.287	-4.583	-0.136	-2.080	0.038
Becker	-3.000	1.078	1.163	-5.114	-0.886	-2.782	0.005
Kaneko	-2.671	1.033	1.068	-4.696	-0.646	-2.585	0.010
Pepperell	-2.823	0.872	0.761	-4.533	-1.113	-3.236	0.001
Monasterio	-3.032	0.791	0.626	-4.583	-1.481	-3.832	0.000
Barbe	-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001
Meta Analysis	-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001

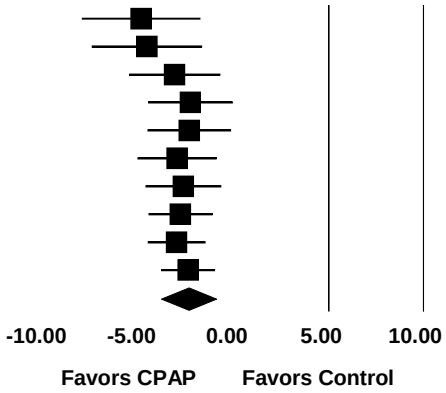
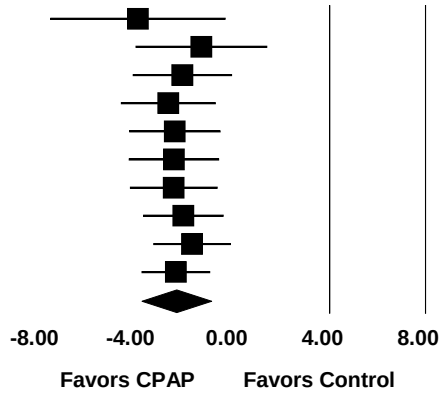


Figure H-50. Sensitivity Analysis 4: Cumulative FEMA – Oldest Study First

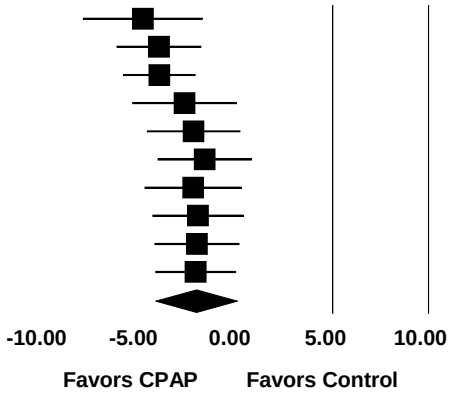
Study Name	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Monasterio	-4.000	1.878	3.528	-7.681	-0.319	-2.130	0.033
Barbe	-1.353	1.413	1.997	-4.122	1.417	-0.957	0.338
Pepperell	-2.146	1.067	1.139	-4.238	-0.055	-2.011	0.044
Becker	-2.737	1.020	1.041	-4.737	-0.738	-2.683	0.007
Kaneko	-2.460	0.982	0.964	-4.384	-0.536	-2.506	0.012
Usui	-2.500	0.970	0.941	-4.402	-0.598	-2.577	0.010
Robinson	-2.505	0.944	0.892	-4.357	-0.654	-2.653	0.008
Campos-Rodriguez	-2.106	0.869	0.755	-3.809	-0.403	-2.423	0.015
Hui	-1.744	0.837	0.701	-3.384	-0.103	-2.083	0.037
Coughlin	-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001
	-2.417	0.742	0.551	-3.872	-0.962	-3.256	0.001



Meta Analysis

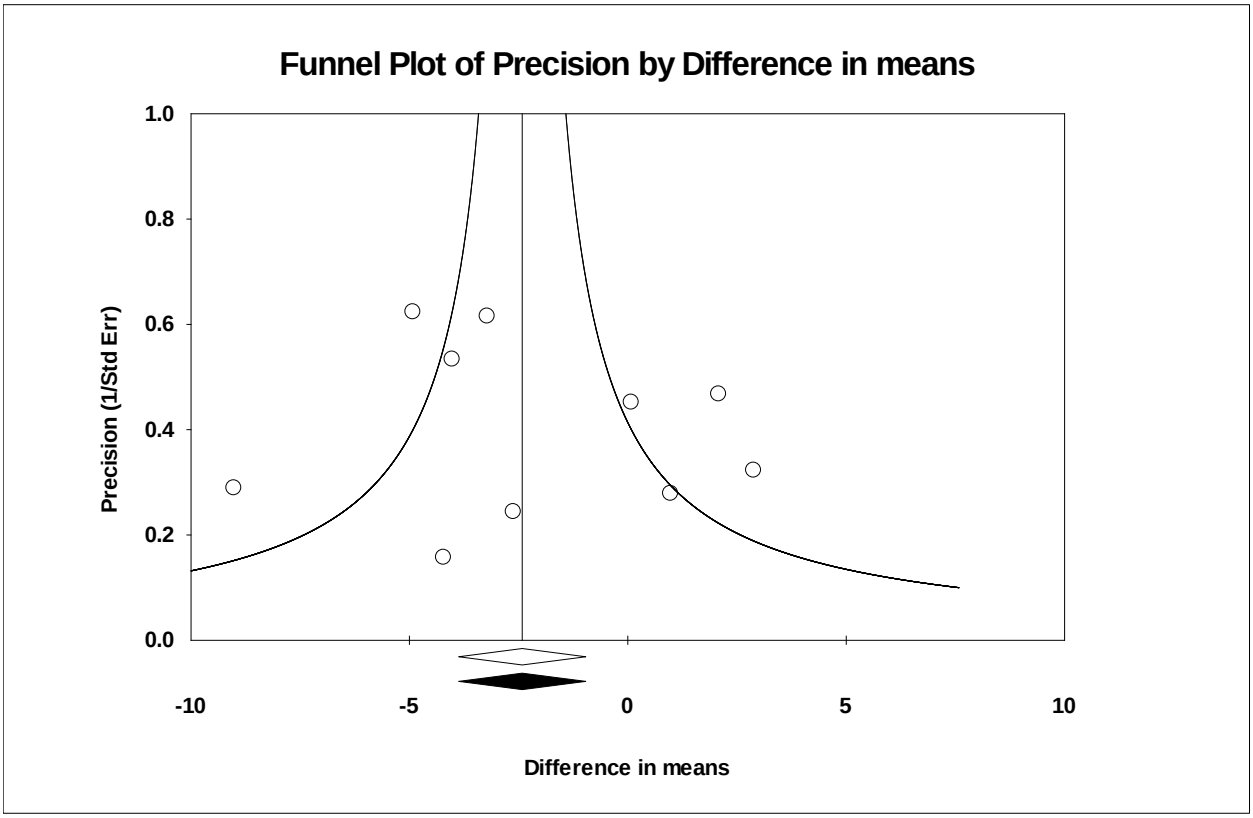
Figure H-51. Sensitivity Analysis 5: Cumulative FEMA – Highest Weighted Study First

Study Name	Point	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Coughlin	-4.900	1.607	2.582	-8.049	-1.751	-3.049	0.002
Pepperell	-4.061	1.144	1.308	-6.303	-1.820	-3.551	0.000
Monasterio	-4.045	0.977	0.954	-5.959	-2.130	-4.140	0.000
Barbe	-2.725	1.407	1.980	-5.483	0.033	-1.936	0.053
Campos-Rodriguez	-2.251	1.256	1.578	-4.713	0.211	-1.792	0.073
Hui	-1.676	1.267	1.605	-4.159	0.808	-1.322	0.186
Becker	-2.275	1.306	1.706	-4.835	0.285	-1.742	0.082
Kaneko	-2.025	1.228	1.509	-4.433	0.382	-1.649	0.099
Robinson	-2.077	1.141	1.302	-4.313	0.160	-1.820	0.069
Usui	-2.146	1.088	1.184	-4.279	-0.013	-1.972	0.049
	-2.146	1.088	1.184	-4.279	-0.013	-1.972	0.049



Meta Analysis

Figure H-52. Sensitivity Analysis 6: Publication Bias Tests (Tweedie and Duval)



Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-2.41725	-3.87221	-0.96228	-2.14603	-4.27892	-0.01314	16.54014
Adjusted values	0	-2.41725	-3.87221	-0.96228	-2.14603	-4.27892	-0.01314	16.54014

Figure H-53. Sensitivity Analysis 7: Cumulative REMA

Study Name	Difference in Means	Standard Error	Variance	Lower Limit	Upper Limit	z-Value	p-Value
Usui	-4.200	6.408	41.061	-16.759	8.359	-0.655	0.512
Robinson	-2.600	4.119	16.966	-10.673	5.473	-0.631	0.528
Kaneko	1.000	3.605	12.999	-6.067	8.067	0.277	0.782
Becker	-9.000	3.474	12.066	-15.808	-2.192	-2.591	0.010
Hui	2.900	3.111	9.678	-3.197	8.997	0.932	0.351
Campos-Rodriguez	0.100	2.219	4.926	-4.250	4.450	0.045	0.964
Barbe	2.100	2.145	4.601	-2.104	6.304	0.979	0.328
Monasterio	-4.000	1.878	3.528	-7.681	-0.319	-2.130	0.033
Pepperell	-3.200	1.628	2.651	-6.391	-0.009	-1.965	0.049
Coughlin	-4.900	1.607	2.582	-8.049	-1.751	-3.049	0.002
Meta Analysis	-2.146	1.088	1.184	-4.279	-0.013	-1.972	0.049