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SENT VIA EMAIL TO: epc@ahrq.hhs.gov

Re: Draft Technology Assessment – "Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea"

Dear Dr. Berliner:

The undersigned organizations wish to comment on the draft technology assessment entitled, "Continuous Positive Airway Pressure (CPAP) Treatment for Obstructive Sleep Apnea (OSA)," prepared for the Evidenced-based Practice Center (EPC) program at AHRQ at the request of the Centers for Medicare & Medicaid Services (CMS). We commend CMS for requesting, and AHRQ for initiating, this evidence review. Periodic evidenced-based reviews of technology are essential to inform clinical practice, enhance delivery of patient care, and focus research priorities. However, evidence-based reviews have limitations in informing policy decisions, often based on their scope, requiring the need to look at additional evidence for a more complete picture and inform policy recommendations. As discussed in this response, we believe that most patients and clinicians would place a high value on some outcomes, excessive sleepiness in particular, that this draft report appears

to indicate are not clinically important. We request that if AHRQ wishes to draw conclusions about clinically important outcomes, the technology assessment should assess the evidence for all outcomes that patients and clinicians are likely to consider important.

The AHRQ draft report performed a comprehensive review to primarily address two key areas: 1) the effectiveness of CPAP therapy to improve clinically significant long-term outcomes in patients with OSA and 2) the evidence that measures of sleep-disordered breathing are valid surrogate or intermediate measures for clinically significant outcomes. Overall, the evidence-based review focused specifically on "long-term outcomes" and conveys the general state of knowledge regarding the effects of CPAP treatment on some clinically significant outcomes (e.g., mortality and cardiovascular events) for people with OSA, describes the limitations of the current literature, and provides recommendations for future studies that the sleep research community should consider. However, the overall message conveyed by the draft report is that there are no significant benefits, short- or long-term, from CPAP treatment, when this conclusion does not reflect the totality of available evidence. We are concerned that the draft, as written, has a high likelihood of being misconstrued and will have detrimental repercussions for the care of millions of Americans with OSA receiving benefit from CPAP therapy now and in the future.

Our specific concerns include:

- **Excessive sleepiness was not considered a clinically important, patient-centered, long-term outcome:** Sleepiness was relegated to a surrogate or intermediate outcome rather than a meaningful, clinically significant outcome of great importance to patients. The consequence of this decision is the absence of analyses that demonstrate the effectiveness of CPAP in improving sleepiness over a period of 6 months or more.
- **Important data on motor vehicle crashes was not considered:** Limiting analyses to only include recent randomized controlled trial (RCT) data assessing the impact of OSA treatment on motor vehicle crashes is worrisome given the major personal and public health implications of this outcome.
- **Improvement in blood pressure was not considered a clinically relevant outcome:** The draft report focused only on the prevention of incident hypertension and normalization of blood pressure but failed to consider blood pressure reduction as a long-term, clinically important outcome.
- **Analyses of AHI as an intermediate outcome had potential limitations:** A suboptimal methodologic approach was used to determine the validity of the apnea-hypopnea index (AHI) as an intermediate or surrogate outcome by examining correlational changes in the AHI with CPAP therapy and changes in clinical outcomes.
- **The future research section did not adequately consider the barriers to conducting RCTs:** Complementary, alternative study designs should be considered for future trials of OSA on long-term outcomes, including in targeted patient groups.
- **The summary statements were unclear:** The language used to summarize the strength of evidence and directionality of effects was difficult to interpret. This creates a strong potential for misinterpretation by non-expert readers.

Given the tremendous policy impact that the final AHRQ report will likely have in the care of patients with OSA, we are asking the AHRQ to carefully consider our detailed comments and consider revising the draft report prior to final publication to avoid misinterpretations or the appearance of bias.

Excessive sleepiness was not considered a clinically important, patient-centered, long-term outcome.

A critical concern is that the AHRQ report does not acknowledge that CPAP is an effective treatment for OSA-related symptoms, in particular, excessive daytime sleepiness (referred to as excessive sleepiness in this response). Rather, the statement made repeatedly throughout the draft is that CPAP has no impact on *"long-term, clinically important outcomes."* Although the AHRQ report ultimately acknowledges the strong evidence for the impact of CPAP on excessive sleepiness, it was only recognized at the end of the report (see page 118 of the draft report) with the following statement: *"The generally low SoE regarding the use of CPAP to prevent long-term clinical outcomes (for most outcomes) is in contrast with high SoE of the effect of CPAP to improve AHI and other sleep and symptom measures, as evaluated by ESS,"* and cited two reviews, one of which was authored by the AHRQ.[1, 2]

Fundamental limitations of the current draft are: 1) the failure to consider excessive sleepiness as an important, long-term clinical outcome, 2) not acknowledging the clear symptom benefits, particularly excessive sleepiness, derived with CPAP treatment from the outset in the draft report, and 3) minimizing the importance of shorter-term studies as discussed further below. By not acknowledging or presenting this information, AHRQ gives the non-expert reader the impression that CPAP has no important, long-term, clinically important benefits.

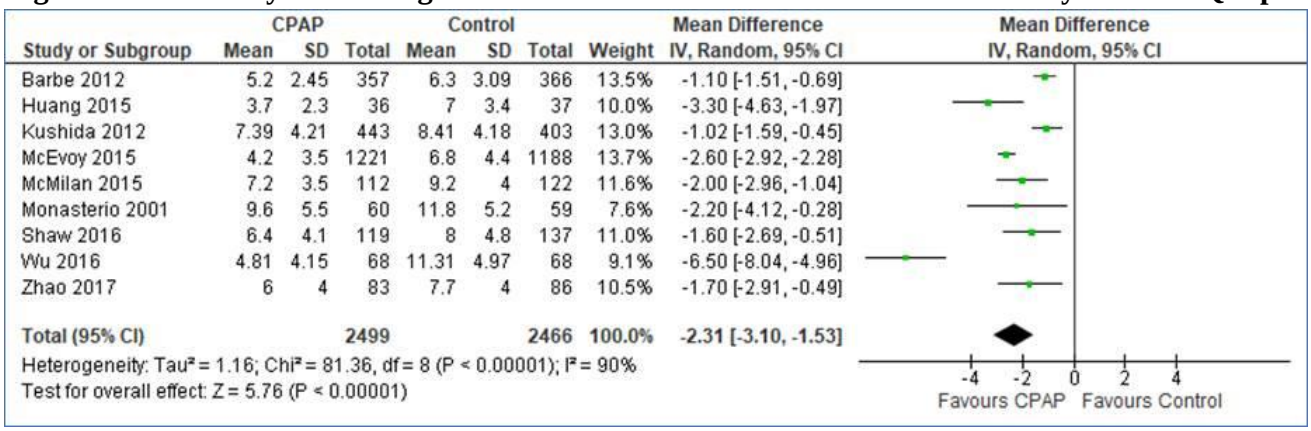
Another major limitation of the draft is that excessive daytime sleepiness (measured by the Epworth Sleepiness Scale, ESS) is exclusively viewed as an intermediate or surrogate outcome, that *"…may be effective to improve symptoms (as measured by the ESS) but these effects do not impact clinical outcomes"* (see page 114 of the draft report). Although the presence of excessive sleepiness may contribute to changes in mood, cognition, and quality of life in OSA patients, excessive sleepiness is a key clinically important, patient-centered outcome for people with OSA, just as relief of arthritic pain is considered a clinically important outcome and a target for treatment of arthritis. Excessive sleepiness is by far the most common daytime, OSA-related symptom for which patients seek treatment and is the strongest clinical indication for prescription of CPAP by clinicians. Furthermore, daytime sleepiness is a major determinant of patients' acceptance of, and adherence to, CPAP over the long-term.[3, 4]

A premise of the draft is that evidence from short-term studies is not relevant for long-term benefits with CPAP treatment, which is another limitation of the report. The AHRQ report relegates the relief of OSA symptoms, such as excessive sleepiness, as a "short-term benefit" of OSA therapy. However, this patient-centric benefit is a long-term, clinically important effect, which is dependent upon continued adherence to CPAP therapy. Excessive sleepiness predictably recurs upon interruption of CPAP in the clinical setting and has been demonstrated in studies implementing 1-2 weeks of CPAP withdrawal in participants on chronic CPAP therapy.[5, 6] We believe that a more accurate characterization of the evidence is that CPAP improves excessive sleepiness when used, and patients must continue CPAP long-term to continue to derive this benefit.

Short and long-term studies have clearly demonstrated the benefits of CPAP in improving excessive sleepiness. In a recent systematic review and meta-analysis of the effects of CPAP in people with OSA conducted by an American Academy of Sleep Medicine (AASM) Task Force,[7, 8] a meta-analysis of 33 RCTs of at least 4 weeks' duration confined to participants with excessive sleepiness yielded a mean improvement of -2.7 (95% CI: -3.2 to -2.15) points in the ESS with CPAP compared to a control condition (Figure S3 in online supplement).[8] The minimal clinically important difference (MCID) reported for the ESS is considered to be 2.0 (Table 3 in the online supplement).[7] The strength of this evidence led to the recommendation that: "*We recommend that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with excessive sleepiness. (STRONG).*"[7]

The AASM systematic review included trials of less than 6 months duration; however, 10 of the 12 RCTs included in the AHRQ report provide data on the improvement in ESS with CPAP versus a control condition, in studies of at least six months duration. As shown in Figure 1 below, we performed a meta-analysis of nine of the studies in the report (Note: Craig et al 2012[9] did not provide data in a suitable format for analysis but did report a mean treatment effect on ESS of -2.0 (95% CI: -2.6 to -1.4, p <0.001)). Several of these studies excluded participants with at least mild[10] or moderate-severe[11-14] excessive sleepiness based on ESS, including two with the longest follow-up.[11, 12] Despite this, the estimated mean effect of CPAP treatment on ESS was a reduction of -2.31 (95% CI: -3.10 to -1.53) for the nine studies (see Figure 1 of this response). Therefore, studies identified by the draft report provide support for the long-term benefit of CPAP therapy on ESS in patients with OSA, a critical, patient-centered outcome.

Figure 1. Meta-analysis of change in ESS with CPAP based on RCTs identified by the AHRQ report



Note: Mean = follow-up ESS value; mean difference = difference in change in ESS between CPAP and control groups

<u>RECOMMENDATION</u>: To avoid misinterpretation of the AHRQ report, we strongly encourage revisions that acknowledge that excessive sleepiness is a clinically important outcome for patients with OSA. Specifically, we recommend that this be stated at key points within the report, including the abstract, the executive summary, the report findings, discussion, implications, and conclusions. Furthermore, we recommend that a meta-analysis of excessive sleepiness in the included studies be performed with the findings then added to the report. We have no doubt that AHRQ recognizes the value that patients place on the long-term control of symptoms and believe addressing these concerns will minimize misinterpretation that could lead to detrimental policy decisions for patients with OSA.

Important data on motor vehicle crashes (MVCs) was not considered.

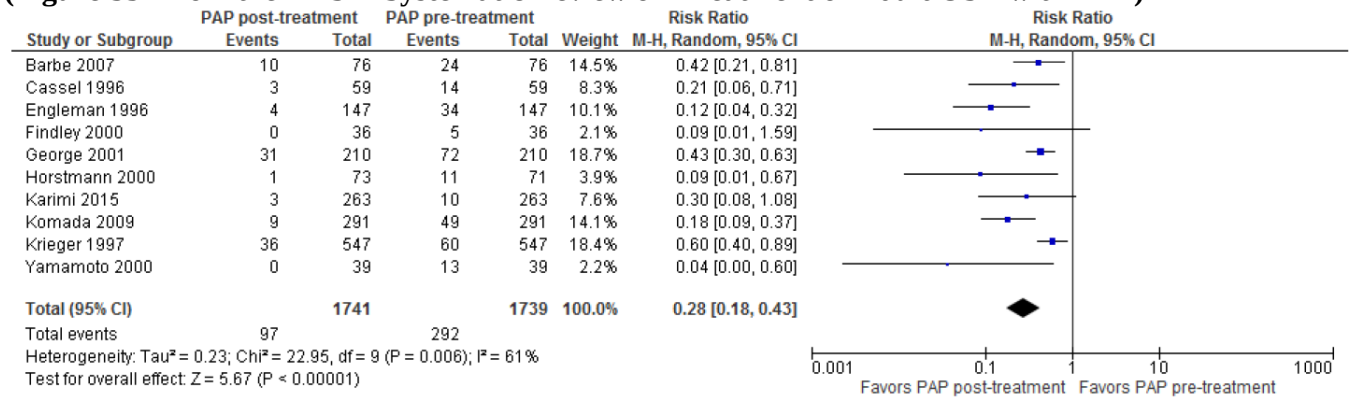
Another impactful long-term clinical outcome, which has received inadequate consideration in this report, is motor vehicle crashes. There is abundant evidence that untreated OSA is associated with an increased rate of car crashes.[15] There are, however, important limitations to relying on RCT data to demonstrate reduction in crashes with CPAP. Specifically, the strong evidence for the effect of CPAP on excessive sleepiness has made it unethical to randomize study participants with severe sleepiness to ineffective treatment for extended periods of time, i.e., 6 months or longer, particularly when the outcome being assessed is potentially fatal. Moreover, as discussed in more detail below, another limitation of the OSA literature is that treatment studies have often not targeted participants with baseline impairment in the outcome of interest who are most likely to benefit from treatment. For MVCs, excessive sleepiness is clearly the greatest predisposing factor such that exclusion of markedly sleepy patients inevitably attenuates any treatment effect.

These limitations are evident in the RCT data on MVCs presented (see pages 64-65 of the draft report) from the SAVE[12] and PREDICT[16] studies. The analysis identified no significant reduction with CPAP in either study, although there was a trend to reduction of the annual rate of crashes causing injury in SAVE (RR 0.84 (95% CI: 0.70 to 1.00). Of note, however, neither study was powered for this secondary outcome, and more importantly SAVE excluded patients with moderate-severe sleepiness (ESS >15), and while PREDICT included patients with ESS >9, patients with a history of sleepiness while driving were specifically excluded.

As stated elsewhere in this response, the absence of a high strength of evidence (SoE) in favor of an OSA treatment is not equivalent to evidence against such an effect. Indeed, for a matter of such great patient and public safety concern, alternate study designs are clearly required, but in the interim, consideration needs to be given to "lower levels" of evidence where available. Two recent meta-analyses[8, 17] have examined data from non-randomized comparative studies (NRCS) on the effect of CPAP treatment of OSA on motor vehicle crashes and yielded very similar findings. The results of the most recent meta-analysis[8] are summarized in the Forest plot below. The 10 studies included consisted mostly of pre- to post-CPAP comparisons for single groups of patients conducted prior to 2010 (and thus did not meet eligibility criteria for the NRCS analyses (see Appendix of draft report, page A8)). However, follow-up in these studies ranged from 2 years before to 0.5 – 6.0 years after enrollment, thus evaluating the long-term impact of OSA treatment. The rate of MVCs was strikingly reduced following CPAP treatment, with an overall risk ratio of 0.28 (95% CI: 0.18 to 0.43).[8] The AASM Task Force established a risk ratio MCID of 0.9 *a priori* for this outcome, thus this finding was deemed highly clinically significant.[8] The methodologically strongest of these studies[18] compared crash rates for 210 patients with OSA before and after CPAP treatment to population control rates during the same time period, with adjustment for annual distance driven and verification of crashes from transport authority records. These authors reported a risk ratio of 0.43 (95% CI: 0.30 to 0.63) for MVCs following CPAP therapy, similar to the overall point estimate.

These data have been considered to be sufficiently compelling to inform recommendations and policies by scientific societies and government transportation agencies for both non-commercial and commercial drivers.[19, 20] Furthermore, this evidence has been translated into a policy change for OSA screening and treatment by commercial trucking agencies, and subsequently has been shown to reduce MVCs among CPAP adherent drivers.[21, 22]

Figure 2. Meta-analysis of PAP pre-treatment vs. PAP post-treatment (MVC Risk Ratio) from NRCS (Figure S51 from the AASM Systematic Review on Treatment of Adult OSA with PAP)[8]



While this body of data may not have met the eligibility criteria for NRCS inclusion set by the report authors, in view of the methodologic considerations discussed above and the patient benefit and public safety implications of these studies:

<u>RECOMMENDATION</u>: We strongly recommend that the search and inclusion criteria for the outcome of motor vehicle crashes in this report be modified to include non-randomized cohort and control studies both prior to and since 2010 for the evaluation of evidence regarding the effect of CPAP on reducing motor vehicle crashes. In addition, the limitations of this analysis, which included the review of studies that excluded sleepy patients and did not consider alternative study designs, should be discussed in the final AHRQ report.

Improvement in blood pressure was not considered a clinically relevant outcome.

We are also concerned about the AHRQ report's approach in evaluating hypertension as a long-term clinical outcome. The draft narrowly focused on the development or resolution of hypertension, which led to the identification of only one RCT for each outcome. This was surprising as we were able to identify one additional study that should have met the report's inclusion criteria (i.e., a NRCS, which uses modelling or other analytical methods to minimize confounding).[23] The study by Marin et al was a prospective cohort study of almost 1900 participants without hypertension, and with and without OSA, followed for a median of 12.2 years for the development of incident hypertension. The study found a reduced risk of incident hypertension (HR 0.71; 95% CI: 0.53 – 0.94) in participants with OSA treated with CPAP compared to those without OSA. In contrast, participants who were ineligible for CPAP, declined CPAP, or were non-adherent to CPAP had a higher risk of incident hypertension. Although the AHRQ report did identify this study, it was excluded in the context of key clinical question 2 (KCQ2) but does not appear to have been evaluated for KCQ1 (see Appendix of draft report, page B-6).

<u>RECOMMENDATION</u>: We recommend that the authors of the draft report re-evaluate this study for inclusion.

The report concludes that, due to the limited number of studies, there is *"insufficient evidence to determine the effect of CPAP on risk of incident HTN or reversion to normotension."* By limiting the focus to the development or resolution of hypertension, the AHRQ report ignores the salient outcome of the magnitude of blood pressure (BP) reduction, which can have important patient-level benefits (e.g., reduction in the number of BP medications) and population-level benefits (e.g., reduction in mortality and cardiovascular outcomes).[24]

In focusing on the development or resolution of hypertension, the AHRQ report fails to acknowledge that hypertension is multi-factorial in etiology with only some intermediate pathways potentially affected by CPAP treatment. While a single anti-hypertensive drug may be expected to lower BP to normal levels in some patients with mild hypertension, it would not be expected to either resolve or prevent new hypertension in all patients. Thus, the effect of CPAP in mitigating OSA and improving hypertension is expected to vary considerably between individuals with studies demonstrating that hypertension phenotype (e.g., uncontrolled, resistant, or refractory hypertension; see Appendix, Table 1), younger age, the presence of excessive sleepiness, greater severity of OSA, and higher adherence to CPAP are important factors in predicting CPAP-induced lowering of BP.[25-28]

The Eighth Joint National Committee's ("JNC 8") 2014 Evidenced-Based Guideline for the Management of High Blood Pressure in Adults[29] stated that the *"main goal of hypertension treatment is to attain and maintain goal blood pressure."* An important observation by the report is that one treatment is often inadequate to maintain full control, and the treatment regimen must be adjusted as needed. In clinical practice, hypertension is managed by a combined approach involving weight loss, exercise, reducing salt intake, drug therapy and other interventions, including CPAP in patients with hypertension and OSA. A multi-modality approach is necessary as the anti-hypertensive effect of any single, isolated intervention is modest, variable, and unpredictable. Indeed, even with a multi-modal approach, less than half (43.5%) of patients have adequately

controlled hypertension.[7, 8, 30] Thus, there has been no BP threshold ever established, to our knowledge, that is required to approve effective anti-hypertensive therapy. By limiting evaluation of the benefit of CPAP in patients with OSA to the prevention or resolution of hypertension, the AHRQ report effectively holds CPAP to a different standard than anti-hypertensive pharmacotherapy. With this standard, there would be no approved treatments for hypertension. Therefore, what is critical is to demonstrate an independent blood pressure lowering effect attributable to a single specific therapy, in the context of RCTs, as has been demonstrated in patients with hypertension and OSA treated with CPAP.[7, 8, 30]

Two recent meta-analyses with similar inclusion criteria have evaluated the effects of CPAP compared to control on blood pressure.[7, 8, 30] Both systematic reviews found clinically significant reductions in blood pressure with CPAP. One review[30] reported a mean reduction of -2.6 (95% CI: -3.6 to -1.6) mm Hg for systolic BP and -2.1 (95% CI: -2.8 to -1.4) for diastolic BP from 33 studies ranging in duration from 4 – 52 weeks (with the exception of Huang et al[11] which had an even longer follow-up). OSA has also been established to impair nocturnal BP dipping,[31] the absence of which in cardiovascular studies has been associated with end-organ damage and cardiovascular and cerebrovascular events.[32-35] In the AASM systematic review, the impact of CPAP on nocturnal BP was evaluated in 14 studies. Treatment with CPAP resulted in a mean decrease of -4.2 (95% CI: -6.0 to -2.5) mm Hg for systolic BP and -2.3 (95% CI: -2.7 to -0.9) for diastolic BP (see supplemental figures S10-S11 in the AASM systematic review[8]). As shown in Appendix, Table 1 of this response, reductions in BP were more pronounced when only patients with hypertension and OSA were randomized. The evidence for clinically significant reduction in BP with CPAP treatment in OSA led to the AASM Clinical Practice Guideline recommendation: *"We suggest that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with comorbid hypertension. (CONDITIONAL)."*[7]

While many of the studies highlighted in this response are shorter than the minimum 1-year duration required by the AHRQ draft report, there is evidence that the BP-lowering effect of CPAP is maintained long-term. For example, 2 weeks of CPAP withdrawal in patients with OSA on long-term CPAP therapy resulted in significant increases in blood pressure.[5] In addition, a large body of cardiovascular literature has demonstrated that sustained reductions in BP by 1-4 mm Hg with anti-hypertensive therapy translates into meaningful long-term cardiovascular risk reduction.[24, 36-38]

We recognize that very large, multi-center studies, with follow-up over several years will ultimately be required to demonstrate the direct impact of BP lowering by CPAP on clinically important cardiovascular outcomes. However, there is every reason to anticipate that BP reduction effects reported with CPAP will be significant based on the above discussion. In the interim, the AHRQ draft report should not misconstrue the absence of evidence for the long-term benefit of CPAP as evidence of absence of a benefit. Furthermore, we view the short-term effect of BP lowering as being highly relevant for long-term clinically relevant outcomes in OSA.

<u>RECOMMENDATION</u>: We, therefore, strongly recommend that the AHRQ report be revised to include analyses of long-term data from RCTs and NRCS on changes in blood pressure with CPAP treatment for patients with OSA.

Analyses of AHI as an intermediate outcome had potential limitations.

Two of the stated key clinical questions (KCQs) addressed by the draft report were whether: 1) currently utilized measures of sleep-disordered breathing (e.g., the apnea-hypopnea index; AHI) are valid surrogate or intermediate measures for clinically significant outcomes (KCQ2) and 2) there is within-study concordance between the AHI and sleepiness (using the ESS) and clinically significant outcomes. After conducting analyses, the AHRQ report concluded that the *"evidence base neither supports nor refutes whether commonly*

used measures (AHI, oxygen desaturation index [ODI], ESS) are valid intermediate or surrogate measures for long-term clinical outcomes" (see page 126 of the draft report), therefore, conclusions could not be drawn regarding these questions. We concur with the AHRQ report that there were limited data in the available literature to address the goal of the KCQ. However, we respectfully disagree with some aspects of the framework established to address this specific KCQ, and strongly encourage that revisions to the report consider proposed alternative approaches and/or incorporate elements of the below comments in the section titled "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" (see page 107 of the draft report).

To address these questions, the methods employed were to determine if a change in the AHI in response to CPAP correlated with a change in clinical outcome. We would argue that this approach is flawed and does not provide needed information regarding a potential dose-response effect between reductions in AHI and improvements in clinical outcome since CPAP adherence was not accounted for.

CPAP is prescribed to patients with OSA to essentially minimize the AHI and improve clinical outcomes. CPAP is effective for the goal of minimizing the AHI,[8] particularly if utilized for the entire period of sleep. Thus, reductions in AHI with CPAP treatment are likely to be a function of the baseline severity but should not be used in determining whether the AHI is an appropriate intermediate or surrogate outcome for clinical outcomes. The approach used in the report primarily reflects the baseline severity of OSA, but does not take into account adherence to, or the "dose" of CPAP, that could influence the particular clinical outcome analyzed.

CPAP is an imperfect therapy, and like most treatments, adherence is variable. We propose at least two more appropriate approaches for examining a dose-response relationship between changes in AHI and any clinical outcome be considered. First, one could examine the extent to which CPAP alleviates the AHI, accounting for the duration of CPAP use as a proportion of total sleep time. At least two measures have been described, the mean disease alleviation index[39] and determination of an effective AHI,[40, 41] both of which account for average CPAP use relative to total sleep duration. Correlation of either of these metrics with changes in clinical outcomes would more directly assess potential dose-response relationships between changes in AHI and clinical outcomes.

A second approach is to examine the relationship between hours of CPAP use and improvements in clinical outcomes. This approach has been used in at least two previously published studies.[42, 43] In both studies, a dose-response relationship was found between hours of CPAP use and reductions in subjective sleepiness. In one of the studies,[43] a dose-response relationship was found between hours of CPAP use and measures of objective and subjective sleepiness, as well as functional status, with a greater proportion of patients achieving normal functioning with longer nightly CPAP use. However, these studies would not have been included in the draft report as the studies were of 3 months duration, rather than the minimum of 6 months that the draft report required.

Finally, we are concerned that the primary analysis performed to determine whether the AHI is a valid mediator of clinical outcomes is flawed because of the singular focus on long-term studies of 6 months or more. Short-term studies can provide valuable information as to whether a measure such as AHI is a valid intermediate outcome for some longer-term clinical outcomes. Short-term studies are more likely to be studies of efficacy as participants are more likely to maintain adherence over shorter periods. In contrast, longer-term studies are more likely to be studies of effectiveness, reflecting more "real world" conditions, with variable use of a particular therapy. As an example, in the largest RCT included in the AHRQ report, the SAVE trial, mean CPAP adherence was 4.4 ± 2.2 h/night at the first month and fell to 3.3 ± 2.3h after a mean follow-up of 3.7 years.

The AHRQ draft report provides an excellent description of ideal study designs to establish the validity of mediator and surrogate measures and provides specific examples for researchers in this field to consider. However, as described in this section, we believe that the approach used would not have allowed the AHRQ to appropriately answer the question posed. We recognize that these analyses have not been widely implemented to date; however, there is a need to encourage appropriate study designs.

RECOMMENDATION: Therefore, we strongly recommend that the draft report be revised to acknowledge the limitations of the analyses performed using change in AHI as an intermediate measure, acknowledge the importance of CPAP adherence in examining dose-response relationship with short- and long-term outcomes, and incorporate the alternative approaches described in the section titled "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" (see page 107 of the draft report).

The future research section did not adequately consider the barriers to conducting RCTs.

The AHRQ draft report provides a strong rationale and useful suggestions for future studies evaluating the long-term benefit of CPAP therapy. However, we believe that the recommendations put forth for specific future studies are incomplete. The draft report does not fully recognize the challenges in this area and the needs to move research on OSA forward. The challenges are related to the heterogeneity of the disorder and the reluctance of patients and physicians to risk randomization into no treatment, given the known symptomatic benefits of CPAP including reductions in excessive sleepiness. There is an outstanding opportunity for the AHRQ report to have a positive, major impact for the research community by providing a more complete roadmap for research into OSA treatment.

The specific recommendations we propose be integrated into the section on future research include discussion of:

1. Potential challenges in conducting RCTs and the need for alternative trial designs, such as adaptive trials and studies of CPAP withdrawal.
2. Alternative non-randomized study designs, including carefully designed propensity score matching studies, when RCTs may not be possible.
3. Studies needed to predict outcomes using molecular biomarkers and genetic markers.
4. The need to recruit and study patients who will likely benefit from CPAP for a specific outcome.
5. Specific studies to establish successful interventions which promote long-term adherence to therapy.

We provide further rationale for these recommendations below.

Design of Future RCTs

The draft report advocates for new, larger RCTs; however, the situation is not as simple as the authors of the AHRQ report envisage. Benefits of CPAP with respect to multiple outcomes have been documented in shorter-term studies (see earlier section on sleepiness). The report acknowledges that there is high SoE of CPAP to improve symptoms,[1, 2] such as excessive sleepiness. Given these acknowledged benefits, clinicians in practice and who participate with institutional review boards (IRBs) have been reluctant to have patients participate in randomized studies that include the possibility of receiving no treatment for multiple years, as would be required for RCTs to assess long-term benefits. There are also potential safety concerns, such as an increased risk of motor vehicle crashes[15] in patients with OSA and the potential harm their sleepiness may present to others on the road.

Given that participants enrolled in longer-term RCTs are usually less symptomatic due to referring clinicians not being in equipoise, it is not surprising that CPAP adherence in these studies is much lower than that described in a study of millions of typical clinical patients with OSA.[44] Thus, the trials reviewed in the AHRQ report are not providing evidence that CPAP does not have cardiovascular benefit in patients with OSA. Rather, these studies are providing evidence that CPAP does not have cardiovascular benefits in relatively asymptomatic patients without excessive sleepiness who have poor CPAP adherence (partial treatment). This is not a surprising conclusion.

While designing RCTs to address whether treatment of OSA with CPAP or other interventions improves cardiovascular and other long-term clinically important outcomes will be challenging, strategies to make these study designs more efficient have been described.[45] Specifically, adaptive enrichment designs may be one approach, where through pre-specified interim analyses, more promising at-risk groups (e.g., excessively sleepy, higher nocturnal hypoxemic burden) may be identified, which allow eligibility criteria to be modified to oversample participants in that subgroup. This has the advantage of potentially decreasing both the time needed to complete an RCT and the ultimate sample size required. In addition, SMART (sequential, multiple assignments, randomized trials) designs have also been advocated.[45] This approach allows for non-adherent participants to be subsequently re-randomized to an alternative treatment intervention (e.g., oral appliance therapy, hypoglossal stimulation, surgical intervention, or pharmacotherapy). Such an approach would help optimize adherence to a treatment intervention in order to assess long-term outcomes more adequately.

Randomized trials with a withdrawal design (i.e., withdrawal of treatment) have several benefits that can provide data on the ability of OSA treatments to suppress symptoms and control blood pressure over long periods. Particular outcomes of interest include symptomatic benefit for sleep quality, excessive sleepiness symptoms, nocturia, quality of life of the patient and bedpartner, headaches, concentration and attention, mood and anxiety. Withdrawal studies can provide data on the sustained effects of long-term treatment of OSA in much shorter time frames and at lower costs than a typical randomized trial. They can potentially minimize bias from suboptimal CPAP adherence and incomplete therapeutic effects. They can minimize sample bias by enriching study populations with patients with comorbidities of interest (e.g., hypertension or cognitive impairment) prior to CPAP initiation. Given the shorter time frame, blinded randomization with sham treatment (e.g., sham CPAP) could be performed.

<u>RECOMMENDATION</u>: We recommend that the draft report section on "Future Research" be revised to acknowledge the need for alternative RCT designs as described to determine if treatment of OSA with CPAP or other therapies improves clinically important long-term outcomes.

<u>Propensity Score Matching Studies</u>

When conducting longer-term RCTs is challenging, other study designs should be considered. In this situation, non-randomized, prospective cohort studies with a carefully conducted propensity score matching design may be appropriate.[46] This type of observational design is often used in similar circumstances where RCTs are problematic. Although the AHRQ report gives weight to studies employing propensity score matching, the analyses reviewed were typically conducted post-hoc after the RCT was completed, i.e., this was not the primary design.

The Center for Devices and Radiologic Health (CDRH) of the FDA has accepted well-conducted propensity score designs as the basis for the approval of a number of medical devices,[47, 48] and FDA review statisticians have written extensively concerning best practices.[49, 50] Importantly, these study designs need to control for healthy user and healthy adherer bias.[51-53] Studies indicate, however, that RCTs and observational designs can lead to the same conclusions when applied to the same groups of subjects with the same outcomes.[54, 55]

Moreover, well-conducted propensity score matching studies have been shown to replicate the findings of RCTs at a fraction of the cost.[56]

RECOMMENDATION: There is a major need for well-designed propensity score matching studies addressing, in particular, the major likely confounders and using state-of-the-art analytical strategies. Therefore, we strongly encourage the draft report section on "Future Research" be revised to include discussion of prospective, non-randomized studies with propensity score matching as the primary design.

New Approaches to Define Disease Severity

The authors of the report have appropriately drawn attention to the need for metrics of disease burden rather than event rate. In addition, a fundamental argument against the sole use of the AHI as a measure of disease severity is the low level of correlation with different outcomes of the disorder (e.g., excessive sleepiness and hypertension).[57, 58] A recent report of the Sleep Research Society (SRS)[57] addresses the strengths and weaknesses of the AHI. It emphasizes three potential sources that serve to limit the predictive ability of the AHI:

1) Precision - does the AHI measure accurately the burden of disease?
2) Individual differences in response to OSA
3) Competing (non-OSA) causes of outcomes of interest

As outlined in the SRS report, one should not solely rely on physiological measures to provide prediction of outcomes.[57] We also need to utilize molecular biomarkers[59] and genetic studies to develop polygenetic risk scores. All tools should be initially utilized to provide enhanced prediction of outcomes so that the optimal approach can be developed. It should not simply be based on only physiological measures. There are, however, new physiologic metrics such as hypoxic burden[60] and heart rate response to arousal[61] that have been shown to be predictors of future cardiovascular events. These new metrics need to be more thoroughly investigated.

RECOMMENDATION: With this background, we encourage AHRQ to revise the draft report section on "Future Research" to describe the importance of doing studies with molecular biomarkers (multiple OMIC strategies), genetic markers, and novel physiologic measures to enhance prediction of outcomes.

Specific Patient Populations

There is considerable heterogeneity in patients with OSA both from a clinical symptomatic perspective[62, 63] that affects risk of CV disease[64] and other outcomes from a physiological viewpoint.[65] There is also individual variation in outcomes in patients with this disorder. Thus, future studies should seek to recruit and study individuals who will likely benefit from CPAP for a specific outcome. Examples of this include studying blood pressure changes in patients who are hypertensive, studying the impact of CPAP on neurocognition in patients with observed deficits in cognition before starting therapy, and studying depression changes in patients who are depressed.

RECOMMENDATION: We recommend that the AHRQ report make specific recommendations for studies on selected patient groups. We strongly encourage that the draft report section on "Future Research" be expanded to provide suggestions of specific populations with OSA that should be studied, such as those with depression, anxiety, cognitive impairment, and specific cardiovascular disorders. Stating specific populations that should be studied is an opportunity to advance strategies to obtain the evidence that is needed.

Enhancing CPAP Adherence

Fundamental to studying long-term outcomes of CPAP is to ensure adherence to the therapy. Adherence to CPAP in recent long-term RCTs has been problematic and is not typical of what is found in clinical samples.[44] This likely reflects the relatively asymptomatic nature of subjects who were recruited.[46] In the future research section, the AHRQ report suggests that evidence is needed to address issues of non-adherence and how these issues can be minimized. Although we agree with the draft report's premise, more specific recommendations could be presented to stimulate the research community.

Methods to enhance CPAP adherence can be divided into four broad categories—education at initiation of therapy, behavioral interventions, troubleshooting interactions, and tele-monitoring. Much of the literature on methods to enhance CPAP adherence has only been performed for a few months.[40, 66] There are very limited data on the effects of interventions to enhance CPAP adherence over the long term (e.g., multiple years). There has been a recent review outlining strategies to manage CPAP adherence in clinical trials, with the need to assess the validity and value of this approach for implementation in long-term studies.[67]

RECOMMENDATION: Therefore, we strongly encourage that the section on "Future Research" acknowledges the specific need for studies of CPAP adherence in patients with OSA to optimize strategies for long-term RCTs and NRCS in the treatment of OSA.

The summary statements were unclear.

We are concerned that the language used in the AHRQ report to create summary statements, which integrate the strength of evidence (SoE) with the directionality of effect for each clinical outcome, will be confusing to readers of the report and lead to misinterpretation. For example, there are several statements on outcomes from the executive summary which may confuse the reader, as the statements are presented as "double negatives" (see italics added):

- ". . .there was *low SoE* that CPAP does *not* affect the risk of cardiovascular (CV) death."
- ". . .provide *low SoE* that CPAP does *not* affect the risk of stroke or acute myocardial infarction."
- ". . .there is *low SoE* that CPAP use does *not* affect the risk of all-cause mortality, stroke, myocardial infarction, composite CV outcomes, driving accidents, and incident diabetes."
- ". . .there is *low* SoE that CPAP does *not* yield clinically meaningful changes in depression and anxiety symptoms, cognitive function, or QoL.

RECOMMENDATION: We encourage AHRQ to revise and more clearly state the observations in the report to prevent misinterpretation by first making a statement about the direction of effect and then providing meta-analysis results when available and the level of confidence as follows: *"[CPAP use (does or does not) affect X (show meta-analysis results) (low SOE)]."*

Conclusions

This AHRQ report has the potential to shape future research endeavors and strengthen the medical knowledge base, while improving the care of patients, for which the authors are to be commended. We acknowledge that the current scientific evidence has not resulted in strong evidence regarding the effect of CPAP on improving composite CV outcomes for patients with OSA. However, the methodology chosen by the draft denies the recognition of the powerful effects of CPAP treatment for other outcomes. In the preceding detailed sections and summarized in the following paragraphs, we express our deep concerns regarding the trivialized effect of

CPAP on patient-centered symptoms, such as excessive sleepiness as a long-term outcome, and safety-oriented outcomes such as motor vehicle crashes.

There are further issues regarding the sole focus on incident and normalized blood pressure as CV outcomes, and the correlation of change in AHI to the change in clinical outcomes to validate the AHI as an intermediate measure. In addition, we reviewed the AHRQ discussion on future studies and recommended to especially emphasize the explicit need for alternative study designs, as randomized clinical trials of CPAP may not be possible for some long-term outcomes and may never be reasonably or ethically undertaken for motor vehicle crashes. We are also concerned about the emphasis and language used to provide the conclusions. It should not be the charge of the report to conclude when it is or is not appropriate to *prescribe* CPAP as stated in the abstract: *"The published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes."* The report finally concludes: *"Specifically, with low SoE RCTs do not demonstrate that CPAP affects all-cause mortality, various CV outcomes, clinically important changes in psychosocial measures, or other clinically important outcomes."* The corollary of this statement can also be true in that the low SoE does not confirm that CPAP *did not* demonstrate an effect on various CV outcomes. In other words, the low SoE of evidence for benefit is not evidence of absence of benefit.

Sleepiness is the most common OSA symptom for which patients seek treatment and is the strongest clinical indication for prescription of CPAP by clinicians, and it often determines patients' adherence to long-term therapy. The draft report itself recognized the strong evidence for the impact of CPAP on excessive sleepiness, as noted deep into the report (see pages 117-118 of the draft report): *"The generally low SoE regarding the use of CPAP to prevent long-term clinical outcomes (for most outcomes) is in contrast with high SoE of the effect of CPAP to improve AHI and other sleep and symptom measures, as evaluated by ESS."* We have described that the major limitation of the draft is that excessive daytime sleepiness (measured by the ESS) is exclusively viewed as an intermediate or surrogate outcome, rather than a key clinically important, patient-centered outcome for people with OSA.

We also detailed how non-commercial motor vehicle crash data supported by prior governmental reports have previously concluded that OSA is an important risk factor that CPAP can benefit. Although the body of data may not achieve the SoE thresholds set by the AHRQ report, appropriate conclusions would be made much clearer by a statement reflecting the methodologic limitations inherent in restricting the evidence base to RCT design to address this question. The patient benefit and public safety implications of motor vehicle crashes are also important. The AHRQ report should acknowledge that there is NRCS evidence supporting a CPAP effect on reducing motor vehicle crashes, especially the many studies excluded that were published more than 10 years ago. This could be rectified if the question of effect on motor vehicle crashes included important studies, especially NRCS prior to 2010, and shorter-term studies.

We provided extensive discussion of the direct effect of CPAP on changes in blood pressure in short and long-term studies as well. The authors of the draft report have focused on incident hypertension and normalization of blood pressure. Despite a large body of research on the effect of CPAP on blood pressure, the AHRQ limited their evaluation to one long-term study on incident blood pressure and one on blood pressure normalization. However, hypertension has a multi-factorial etiology with only some of those pathways potentially affected by CPAP treatment. Furthermore, it is also important not to underappreciate evidence that small improvements in individual blood pressure may be profound when looked at across a large population. We recommend that the AHRQ reassess the outcome of blood pressure to include reduction in blood pressure measurements as a clinically significant, long-term outcome.

When examining the AHI as an intermediate outcome, we argued that the chosen method was inappropriate. This approach did not provide needed information regarding a potential dose-response effect between

reductions in AHI and improvements in clinical outcome such as sleepiness, especially since CPAP use was not accounted for. CPAP is very effective for the goal of minimizing the AHI, best when utilized for the entire period of sleep. Thus, changes in AHI with CPAP treatment are more likely to be a function of the baseline severity of OSA for an individual or group. The approach presented in the AHRQ report should not be used in determining whether the AHI is an appropriate intermediate or surrogate measure for clinical outcomes.

As pointed out when we explore the need for future studies, we noted that the AHRQ report provides a very compelling rationale for why more studies to address the impact of CPAP on longer term outcomes are required. This report does not, however, acknowledge the obstacles inherent with randomization of excessively sleepy patients to a control treatment arm, the most obvious example being the risk of motor vehicle crashes. Complementary, alternative study designs should be considered for future trials of OSA on long-term outcomes, including innovative RCT designs, propensity score matching, and targeting specific patient groups. In addition, identifying biomarkers and genetic predictors of risk and response and innovative approaches to promote long-term CPAP adherence are other areas in need of research.

We are concerned for the millions of patients who have benefitted from the long-term treatment of their OSA and those yet to be diagnosed. The AHRQ report should not present the findings in a way that may appear as an indictment of the current practice for OSA treatment, based on the narrow scope of review chosen by AHRQ from the totality of the evidence available and the exclusion of key, long-term clinical outcomes. The draft report, in its current form, does not accurately reflect the long-term clinical, patient-centered benefits of CPAP. Finally, we appreciate the opportunity to present our suggested revisions and would welcome future discussion with AHRQ regarding matters that have such a significant impact on the improvement of care for patients with OSA using CPAP.

Sincerely,

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Appendix

Table 1. Changes in blood pressure with CPAP in different hypertension groups (Adapted from Tables S10-S33 in Patil, et al, *JCSM* 2019 – online supplement)[8]

Patient Type	Measure	Risk Ratio, 95% confidence interval
All patient types	Change in nighttime SBP	-4.21 (-5.96, -2.45)
	Change in nighttime DBP	-2.31 (-3.72, -0.91
	Change in daytime SBP	-2.76 (-4.31, -1.20
	Change in daytime DBP	-1.98 (-3.02, -0.93
	Change in 24-hour SBP	-1.47 (-2.28, -0.66)
	Change in 24-hour DBP	-1.58 (-2.23, -0.93)
	Change in mean 24-hour BP	-2.63 (-3.86, -1.39)
Resistant hypertensive patients	Change in nighttime SBP	-3.26 (-6.11, -0.41)
	Change in nighttime DBP	-2.20 (-4.39, -0.01)
	Change in daytime SBP	-1.54 (-4.47, 1.39)
	Change in daytime DBP	-1.13 (-3.37, 1.12)
	Change in 24-hour SBP	-2.15 (-5.05, 0.75)
	Change in 24-hour DBP	-2.06 (-4.12, -0.00)
Hypertensive patients	Change in nighttime SBP	-3.94 (-6.46, -1.43)
	Change in nighttime DBP	-3.03 (-5.28, -0.79)
	Change in daytime SDP	-2.70 (-4.92, -0.47)
	Change in daytime DBP	-2.40 (-3.88, -0.92)
	Change in 24-hour SBP	-2.53 (-4.30, -0.76)
	Change in 24-hour DBP	-2.23 (-3.42, -1.03)
	Change in mean 24-hour BP	-2.16 (-3.59, -0.72)
Normotensive patients	Change in nighttime SBP	-1.91 (-7.16, 3.34)
	Change in nighttime DBP	-1.00 (-4.38, 2.38)
	Change in daytime SBP	-0.39 (-4.75, 3.97)
	Change in daytime DBP	-0.24 (-2.91, 2.42)

BP=blood pressure, DBP=diastolic blood pressure, SBP=systolic blood pressure

References

1. Balk EM, Moorthy D, Obadan NO, et al. *Diagnosis and Treatment of Obstructive Sleep Apnea in Adults*. Rockville (MD); 2011.
2. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006(3):CD001106.
3. McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med*. 1999;159(4 Pt 1):1108-14.
4. Sunwoo BY, Light M, Malhotra A. Strategies to augment adherence in the management of sleep-disordered breathing. *Respirology*. 2020;25(4):363-71.
5. Schwarz EI, Schlatzer C, Rossi VA, Stradling JR, Kohler M. Effect of CPAP Withdrawal on BP in OSA: Data from Three Randomized Controlled Trials. *Chest*. 2016;150(6):1202-10.
6. Yang Q, Phillips CL, Melehan KL, Rogers NL, Seale JP, Grunstein RR. Effects of short-term CPAP withdrawal on neurobehavioral performance in patients with obstructive sleep apnea. *Sleep*. 2006;29(4):545-52.
7. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2019;15(2):335-43.
8. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *J Clin Sleep Med*. 2019;15(2):301-34.
9. Craig SE, Kohler M, Nicoll D, et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. *Thorax*. 2012;67(12):1090-6.
10. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA*. 2012;307(20):2161-8.
11. Huang Z, Liu Z, Luo Q, et al. Long-term effects of continuous positive airway pressure on blood pressure and prognosis in hypertensive patients with coronary heart disease and obstructive sleep apnea: a randomized controlled trial. *Am J Hypertens*. 2015;28(3):300-6.
12. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med*. 2016;375(10):919-31.
13. Monasterio C, Vidal S, Duran J, et al. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med*. 2001;164(6):939-43.
14. Zhao YY, Wang R, Gleason KJ, et al. Effect of Continuous Positive Airway Pressure Treatment on Health-Related Quality of Life and Sleepiness in High Cardiovascular Risk Individuals With Sleep Apnea: Best Apnea Interventions for Research (BestAIR) Trial. *Sleep*. 2017;40(4).
15. Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. *J Clin Sleep Med*. 2009;5(6):573-81.
16. McMillan A, Bratton DJ, Faria R, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. *Lancet Respir Med*. 2014;2(10):804-12.
17. Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. *Sleep*. 2010;33(10):1373-80.
18. George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax*. 2001;56(7):508-12.

19. Federal Motor Carrier Safety Administration. Obstructive Sleep Apnea and Commercial Motor Vehicle Driver Safety. https://www.fmcsa.dot.gov/sites/fmcsa.dot.gov/files/docs/Sleep-Apnea-Final-Executive-Summary-prot.pdf Accessed April 21, 2021.
20. Gurubhagavatula I, Sullivan S, Meoli A, et al. Management of Obstructive Sleep Apnea in Commercial Motor Vehicle Operators: Recommendations of the AASM Sleep and Transportation Safety Awareness Task Force. *J Clin Sleep Med*. 2017;13(5):745-58.
21. Burks SV, Anderson JE, Bombyk M, et al. Nonadherence with Employer-Mandated Sleep Apnea Treatment and Increased Risk of Serious Truck Crashes. *Sleep*. 2016;39(5):967-75.
22. Garbarino S, Guglielmi O, Campus C, et al. Screening, diagnosis, and management of obstructive sleep apnea in dangerous-goods truck drivers: to be aware or not? *Sleep Med*. 2016;25:98-104.
23. Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012;307(20):2169-76.
24. Rose G. Strategy of prevention: lessons from cardiovascular disease. *Br Med J (Clin Res Ed)*. 1981;282(6279):1847-51.
25. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA*. 2013;310(22):2407-15.
26. Martinez-Garcia MA, Gomez-Aldaravi R, Soler-Cataluna JJ, Martinez TG, Bernacer-Alpera B, Roman-Sanchez P. Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. *Eur Respir J*. 2007;29(5):951-7.
27. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med*. 2012;8(5):587-96.
28. Pengo MF, Soranna D, Giontella A, et al. Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis. *Eur Respir J*. 2020;55(5).
29. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-20.
30. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs Mandibular Advancement Devices and Blood Pressure in Patients With Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA*. 2015;314(21):2280-93.
31. Cuspidi C, Tadic M, Sala C, Gherbesi E, Grassi G, Mancia G. Blood Pressure Non-Dipping and Obstructive Sleep Apnea Syndrome: A Meta-Analysis. *J Clin Med*. 2019;8(9).
32. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension*. 2011;57(1):3-10.
33. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension*. 2001;38(4):852-7.
34. Ohkubo T, Hozawa A, Nagai K, et al. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens*. 2000;18(7):847-54.
35. Verdecchia P, Schillaci G, Guerrieri M, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation*. 1990;81(2):528-36.
36. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-13.
37. Turnbull F, Blood Pressure Lowering Treatment Trialists C. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362(9395):1527-35.

38. Whelton SP, McEvoy JW, Shaw L, et al. Association of Normal Systolic Blood Pressure Level With Cardiovascular Disease in the Absence of Risk Factors. *JAMA Cardiol*. 2020;5(9):1011-18.
39. Grote L, Hedner J, Grunstein R, Kraiczi H. Therapy with nCPAP: incomplete elimination of Sleep Related Breathing Disorder. *Eur Respir J*. 2000;16(5):921-7.
40. Bakker JP, Weaver TE, Parthasarathy S, Aloia MS. Adherence to CPAP: What Should We Be Aiming For, and How Can We Get There? *Chest*. 2019;155(6):1272-87.
41. Bianchi MT, Alameddine Y, Mojica J. Apnea burden: efficacy versus effectiveness in patients using positive airway pressure. *Sleep Med*. 2014;15(12):1579-81.
42. Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep*. 2011;34(1):111-9.
43. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*. 2007;30(6):711-9.
44. Cistulli PA, Armitstead J, Pepin JL, et al. Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data. *Sleep Med*. 2019;59:114-16.
45. McEvoy RD, Sanchez-de-la-Torre M, Peker Y, Anderson CS, Redline S, Barbe F. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep*. 2021;44(4).
46. Pack AI, Magalang UJ, Singh B, Kuna ST, Keenan BT, Maislin G. Randomized clinical trials of cardiovascular disease in obstructive sleep apnea: understanding and overcoming bias. *Sleep*. 2021;44(2).
47. U.S. Food and Drug Administration. Approval Order - M6-C Artificial Cervical Disc (Spinal Kinetics LLC). https://www.fda.gov/medical-devices/recently-approved-devices/m6-ctm-artificial-cervical-disc-p170036. Accessed April 22, 2021.
48. U.S. Food and Drug Administration. Simplify Cervical Artificial Disc - P200022. https://www.fda.gov/medical-devices/recently-approved-devices/simplify-cervical-artificial-disc-p200022. Accessed April 22, 2021.
49. Li H, Mukhi V, Lu N, Xu Y-L, Yue LQ. A Note on Good Practice of Objective Propensity Score Design for Premarket Nonrandomized Medical Device Studies with an Example. *Statistics in Biopharmaceutical Research*. 2016;8(3):282-86.
50. Yue LQ. Statistical and regulatory issues with the application of propensity score analysis to nonrandomized medical device clinical studies. *J Biopharm Stat*. 2007;17(1):1-13; discussion 15-7, 19-21, 23-7 passim.
51. Kinjo M, Chia-Cheng Lai E, Korhonen MJ, McGill RL, Setoguchi S. Potential contribution of lifestyle and socioeconomic factors to healthy user bias in antihypertensives and lipid-lowering drugs. *Open Heart*. 2017;4(1):e000417.
52. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. *J Gen Intern Med*. 2011;26(5):546-50.
53. Silverman SL, Gold DT. Healthy users, healthy adherers, and healthy behaviors? *J Bone Miner Res*. 2011;26(4):681-2.
54. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med*. 2000;342(25):1878-86.
55. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342(25):1887-92.
56. Fralick M, Kesselheim AS, Avorn J, Schneeweiss S. Use of Health Care Databases to Support Supplemental Indications of Approved Medications. *JAMA Intern Med*. 2018;178(1):55-63.
57. Malhotra A, Ayappa I, Ayas N, et al. Metrics of Sleep Apnea Severity: Beyond the AHI. *Sleep*. 2021.
58. Pevernagie DA, Gnidovec-Strazisar B, Grote L, et al. On the rise and fall of the apnea-hypopnea index: A historical review and critical appraisal. *J Sleep Res*. 2020;29(4):e13066.

59. Mullington J, Pack AI, Ginsburg GS. In Pursuit of Sleep-Circadian Biomarkers. *Sleep*. 2015;38(11):1665-6.
60. Azarbarzin A, Sands SA, Taranto-Montemurro L, Redline S, Wellman A. Hypoxic burden captures sleep apnoea-specific nocturnal hypoxaemia. *Eur Heart J*. 2019;40(35):2989-90.
61. Azarbarzin A, Ostrowski M, Hanly P, Younes M. Relationship between arousal intensity and heart rate response to arousal. *Sleep*. 2014;37(4):645-53.
62. Keenan BT, Kim J, Singh B, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep*. 2018;41(3).
63. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J*. 2014;44(6):1600-7.
64. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes. *Am J Respir Crit Care Med*. 2019;200(4):493-506.
65. Zinchuk AV, Jeon S, Koo BB, et al. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. *Thorax*. 2018;73(5):472-80.
66. Weaver TE. Novel Aspects of CPAP Treatment and Interventions to Improve CPAP Adherence. *J Clin Med*. 2019;8(12).
67. Sawyer AM, Wallace DM, Buenaver LF, et al. Where to Next for Optimizing Adherence in Large-Scale Trials of Continuous Positive Airway Pressure? *Sleep Med Clin*. 2021;16(1):125-44.