

How could the USPSTF make this draft Recommendation Statement clearer?

A fundamental concern is the ambiguity in this report in use of both the terms “asymptomatic” and “screening,” neither of which was clearly defined but are terms and concepts that constitute the basis for this report. In particular, the report emphasizes its applicability to “asymptomatic” patients, but never defines how asymptomatic status is ascertained. The report argues against screening of asymptomatic patients but does not describe how asymptomatic patients are identified, nor addresses the more general problem of sleep apnea recognition. It is also not clear if the intent of this recommendation is to evaluate the validity of screening questionnaires, limited monitoring, or more generally, the need for clinical review of symptoms as part of the patient history. Without clarity, the report can exacerbate a “catch-22”: if patients are not asked about symptoms, then sleep apnea-related symptoms such as sleepiness may never be elicited, preventing pursuance of specific screening or testing.

It is a serious flaw to assume that patients who do not spontaneously report symptoms such as sleepiness or snoring are “asymptomatic.” If patients are not explicitly asked about sleep apnea symptoms, it is impossible to know who is asymptomatic. Symptoms that may have developed over many years and/or have social stigma may not be spontaneously self-identified as a “chief complaint”. Patients with sleep apnea commonly report having lived with sleep apnea for many years prior to a diagnosis,¹ indicating the frequency of marked delays in diagnosis.

There is a significant problem of clinician under-recognition of sleep apnea that this report may exacerbate. A failure to recognize sleep apnea in both primary care and high risk clinical settings will contribute to under-diagnosis and delayed treatment of a highly prevalent disorder² with extensive morbidity. There is abundant evidence that clinicians do not regularly consider sleep apnea diagnoses even among high risk patients³⁻⁵. The vast majority of participants in community-based studies who have undergone sleep apnea testing who are found to have an elevated AHI and symptoms were never clinically diagnosed, emphasizing the prevalence of undiagnosed sleep apnea in the general population as well as high risk groups.^{6,7} Furthermore, there is a disproportionate under-recognition of sleep apnea in certain groups, such as women⁸ and ethnic minorities,⁷ and this report can exacerbate health disparities. This report does not specifically address the need to use physiologically and culturally appropriate screening devices for population subgroups, nor recognizes the concern that health disparities may be exacerbated without deliberate strategies for improving sleep apnea recognition across the population.

A more balanced and thorough discussion of risks of untreated sleep apnea is needed to clarify the morbidity of sleep apnea on the myriad aspects of health and well-being. As noted below, numerous observational studies have demonstrated clearly increased incidence rates of cardiovascular disease, stroke, diabetes, and mortality, in a dose-dependent fashion, and after adjusting for the confounders. This report implies that confounders have not been adequately addressed in the literature but this is not supported by the findings of large observational studies of sleep apnea that have adjusted for important confounders.

Given the high prevalence and morbidity of sleep apnea, we recommend that the report explicitly clarify that an appropriate medical history includes ascertainment of symptoms such as sleepiness and snoring and query patients about sleep quality and duration. Furthermore, the

health concerns regarding under-recognition of sleep apnea, in particular in women and minorities, need further emphasis. The negative impact of delayed diagnosis needs discussion.

What information, if any, did you expect to find in this draft Recommendation Statement that was not included?

Statements regarding associated risks of cardiac and cerebrovascular disease and mortality are surprisingly under-stated despite the availability of large cohort studies that have followed individuals in the community for 8 or more years, have systematically assessed sleep apnea and rigorously adjudicated outcomes, and controlled for factors such as BMI and age (which the report implied were residual confounders), with some studies even controlling for conditions in causal pathways such as hypertension⁹⁻¹². Meta-analyses estimate that sleep apnea is associated with a 56% to 220% increased incidence of cardiovascular disease or stroke¹³. Among the outcomes with the strongest associations with sleep apnea is stroke^{10, 14}, a potentially devastating outcome, which requires further recognition in this report.

The USPSTF emphasized the lack of evidence relating change in AHI with change in clinical outcomes. However, numerous studies have shown dose-response associations between AHI (or degree to which AHI is reduced as measured by CPAP use) and intermediate and clinical outcomes (example reports:¹⁵⁻²³). Moreover, the AHI is only one of several clinically derived metrics to assess sleep apnea, and depending on the outcome, other metrics are more responsive, but were not discussed. For example, sleep-related hypoxemia is predictive of degree of improvement in intermediate cardiac endpoints, as well as in clinical outcomes such as diabetes/glucose impairment²⁴, cognitive impairment and risk of dementia²⁵, and mortality²⁶. The report did not discuss the often profound sleepiness and impairment of quality of life in patients with sleep apnea, and the responsiveness of these important patient-reported outcomes²⁷. It is important to clarify that while AHI severity and improvement have been observed in association with subclinical and clinical outcomes, additional metrics too, such as hypoxemia, have been correlated with disease severity, and additional research on optimal predictors of susceptibility and treatment response is needed.

The review of screening instruments omitted relevant literature and inadequately discussed the use of alternative cutoff thresholds for screening, which *should* vary according to the desired ratio of sensitivity to specificity. Given the low risk for sleep apnea screening in face of the high morbidity of the disease, it was surprising that there was no discussion of the value of choosing thresholds that optimize sensitivity, even at the expense of specificity. For example, for the STOP Bang screening questionnaire, there is evidence of how to vary selection of thresholds for screening to achieve targeted levels of sensitivity/specificity for a given population. Relevant studies testing the STOP Bang and Berlin questionnaires were not cited^{28, 29 28}, including research performed in the primary care setting.³⁰ The use of questionnaires in various settings such as in the pre-operative settings^{31, 32}, pregnancy³³, the work place,²⁸ diabetes clinics³⁴, commercial drivers,^{35, 36} and cardiology settings³⁷ were not discussed despite their relevance to primary care or management of high risk patients. Development and validation of sex-specific approaches for sleep apnea screening in over 12,000 individuals have been published,³⁸ underscoring the ability to optimize prediction equations for men and women, but were not cited. Approaches for use of combined questionnaires and monitoring to improve prediction were inadequately discussed^{37, 39}. Data on the OSA-50 questionnaire were omitted. This device, especially when used with simple overnight oximetry, has been reported to have sensitivity and specificity values exceeding 90% in general medical settings³⁹. In a report published in the New

England Journal of Medicine, the Berlin screening questionnaire used in conjunction with a Type 3 home sleep apnea test was used to screen patients attending cardiology clinics, identifying 50% of this sample with moderate-severe sleep apnea, and further showed that treatment with CPAP led to improved blood pressure³⁷. This study-linking screening to home based diagnosis to blood pressure improvement- provides evidence that screening/sleep apnea testing can identify a patient group likely to show beneficial effects when treated with CPAP.

Based on the evidence presented in this draft Recommendation Statement, do you believe that the USPSTF came to the right conclusions? Please provide additional evidence or viewpoints that you think should have been considered.

This report does not clarify the role of screening approaches for sleep apnea, and rather, obscure the value of improving recognition of sleep apnea. It inappropriately focused on the “accuracy” of screening questionnaires, without clearly defining the target population or defining what is meant by “asymptomatic”. The report did not thoroughly consider the use of screening surveys across many clinical settings, such as the pre-operative assessment setting and cardiology settings, and the value of combining questionnaires with oximetry or home testing.

The report’s focus on “symptomatic patients” is a fundamental flaw. It does not address how a clinician will identify a symptomatic patient, which first requires asking key screening questions. There are patient-reported data that symptoms of sleep apnea are experienced for more than 10 years prior to a sleep apnea diagnosis, indicating the frequent occurrence of long diagnostic delays. This report will further aggravate the marked delays of a treatable condition. Given that there is evidence that sleep apnea may be particularly under-diagnosed in certain ethnic groups and in women, there is the additional concern that this report will further aggravate health disparities.

The report under-estimated the strength of evidence linking sleep apnea to cardiac disease, stroke, diabetes and mortality.

The report minimized the potential benefit of screening and treatment, especially on a population level and within subgroups. The statement that the “clinical evidence that small reductions in blood pressure are of unclear significance” is not supported by research showing that even small changes in blood pressure reduce risk of stroke by 5 to 8%.⁴⁰ Average changes in sleepiness and other patient-centered and clinical outcomes also under-estimate effects in susceptible groups.

This report would benefit by highlighting the need for research to identify most efficient screening approaches for given populations and settings, with consideration of different sensitivities of different instruments by sex and in racial and ethnic groups. For example, women often report symptoms of fatigue rather than sleepiness, and are less likely to desaturate with respiratory events. Some groups, such as Chinese Americans, may be several fold more likely to have undiagnosed sleep apnea, than Whites, underscoring the need for culturally sensitive instruments. The need for appropriate tools for the elderly, in women symptoms may vary and who may have problems reporting symptoms due to cognitive deficits, should be mentioned.

What resources or tools could the USPSTF provide that would make this Recommendation Statement more useful to you in its final form?

For this report to have value, it needs to identify how “asymptomatic” vs “symptomatic” individuals are identified. There should be discussion on the approach to “recognition” of sleep apnea, and include applications to diverse clinical settings where primary care is delivered, such as pregnancy, pre-operative settings and cardiology as well as the work place.

Further discussion on how application of different cutoff values for screening instruments would yield different sensitivities and specificities, and the need to identify the appropriate balance given the clinical or public health need, is needed.

The research needs for identifying subgroups most susceptible to sleep apnea and responsive to intervention would be helpful.

The USPSTF is committed to understanding the needs and perspectives of the public it serves. Please share any experiences that you think could further inform the USPSTF on this draft Recommendation Statement.

The conclusion that there is insufficient evidence for OSA screening in asymptomatic adults raises the entire question of what the authors of this report mean by “asymptomatic”. Snoring is the most common symptom of sleep apnea and is present in upwards of 30% of adults, but is often not ascertained in routine clinical encounters. Patients may not identify this symptom because of unawareness that is a symptom of a treatable condition, and these assumptions may be further aggravated by social and cultural differences, potentially exacerbating health disparities. Sleepiness is often under-recognized due to its chronicity, and it is not until a person is treated do they realize how sleepy and impaired they had been.

Through the Sleep Apnea Patient Centered Outcomes Network, data for over 3,000 patients have been collected that indicate delayed diagnoses and treatment are of paramount importance to patients who have struggled with many of the symptoms for years prior to diagnosis¹. This report has the potential to further aggravate this problem. Treated patients often tell us that their doctors never asked about sleep apnea symptoms, especially if they were not obese or male.

Do you have other comments on this draft Recommendation Statement?

Due to the high prevalence and chronicity of symptoms of sleep apnea, such as snoring and sleepiness, especially in some social and cultural backgrounds where snoring is not recognized to be related to health, patients often do not spontaneously report these symptoms. This report may further aggravate health disparities.

Women with sleep apnea are often under recognized due to lack of “classic” symptoms. Emerging data indicate that cardiovascular risk associated with sleep apnea may be even greater in women than men⁴¹; failure to recognize sleep apnea may contribute to health problems and premature mortality.

Note: Comments are provided by the Society for Women's Health Research's (SWHR's) Interdisciplinary Network on Sex and Gender Differences in Sleep. SWHR is a non-profit organization based in Washington D.C. that is widely considered to be the thought leader in advocating for research on biological differences in disease and is dedicated to transforming women's health through science, advocacy, and education. SWHR aims to bring attention to the variety of diseases and conditions that uniquely affect women. Thanks to SWHR's efforts, women are now routinely included in most major medical research studies and scientists are considering biological sex as a fundamental variable in their research.

References

1. Bakker JP, Baker-Goodwin S, Epstein M, Hanes S, Hanson M, Johnston J, Kapur V, Keepnews D, Kontos E, Lowe A, Owens J, Page K, Rothstein N, Redline S. Diagnostic delays and presenting symptoms reported by patients: The sleep apnea patient-centered outcomes network. *Sleep*. 2016:abstract
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177:1006-1014
3. Miller JN, Berger AM. Screening and assessment for obstructive sleep apnea in primary care. *Sleep Med Rev*. 2015;29:41-51
4. Navalkele DD, Barlinn K, Minagar A, Chernyshev OY. Exploration of screening practices for obstructive sleep apnea in stroke medical community: A pilot study. *Pathophysiology*. 2016;23:105-109
5. Surani S. Are diabetic patients being screened for sleep related breathing disorder? *World J Diabetes*. 2013;4:162-164
6. Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. Underdiagnosis of sleep apnea syndrome in u.S. Communities. *Sleep Breath*. 2002;6:49-54.
7. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcantara C, Jackson CL, Williams MA, Redline S. Racial/ethnic differences in sleep disturbances: The multi-ethnic study of atherosclerosis (mesa). *Sleep*. 2014
8. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. *Am J Respir Crit Care Med*. 1994;149:722-726.
9. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The sleep heart health study. *Circulation*. 2010;122:352-360
10. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, Ali T, Lebowitz M, Punjabi NM. Obstructive sleep apnea-hypopnea and incident stroke: The sleep heart health study. *Am J Respir Crit Care Med*. 2010;182:269-277
11. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: A prospective cohort study. *PLoS Med*. 2009;6:e1000132
12. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378-1384
13. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: A systematic review and meta-analysis. *Circulation. Cardiovascular quality and outcomes*. 2012;5:720-728

14. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med.* 2005;353:2034-2041
15. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med.* 2002;165:670-676
16. Lavie LPALP. Plasma homocysteine levels in obstructive sleep apnea : Association with cardiovascular morbidity. *Chest.* 2001;120:900-908
17. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: A 7-year follow-up. *Am J Respir Crit Care Med.* 2002;166:159-165
18. Barbe F, Duran-Cantolla J, Capote F, de la Pena M, Chiner E, Masa JF, Gonzalez M, Marin JM, Garcia-Rio F, de Atauri JD, Teran J, Mayos M, Monasterio C, del Campo F, Gomez S, de la Torre MS, Martinez M, Montserrat JM. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med.* 2010;181:718-726
19. Zhao YY, Blackwell T, Ensrud KE, Stone KL, Omachi TA, Redline S. Sleep apnea and obstructive airway disease in older men: Outcomes of sleep disorders in older men study. *Sleep.* 2016
20. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S. Association of nocturnal arrhythmias with sleep-disordered breathing: The sleep heart health study. *Am J Respir Crit Care Med.* 2006
21. Seif F, Patel SR, Walia H, Rueschman M, Bhatt DL, Gottlieb DJ, Lewis EF, Patil SP, Punjabi NM, Babineau DC, Redline S, Mehra R. Association between obstructive sleep apnoea severity and endothelial dysfunction in an increased background of cardiovascular burden. *J Sleep Res.* 2013
22. Walia HK, Li H, Rueschman M, Bhatt DL, Patel SR, Quan SF, Gottlieb DJ, Punjabi NM, Redline S, Mehra R. Association of severe obstructive sleep apnea and elevated blood pressure despite antihypertensive medication use. *J Clin Sleep Med.* 2014;10:835-843
23. Javaheri S, Somers VK. Cardiovascular diseases and sleep apnea. *Handb Clin Neurol.* 2011;98:327-345
24. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep disordered breathing, glucose intolerance, and insulin resistance: The sleep heart health study. *Am J Epidemiol.* 2004;160:521-530.
25. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *Jama.* 2011;306:613-619
26. Gami AS, Olson EJ, Shen WK, Wright RS, Ballman KV, Hodge DO, Herges RM, Howard DE, Somers VK. Obstructive sleep apnea and the risk of sudden cardiac death: A longitudinal study of 10,701 adults. *Journal of the American College of Cardiology.* 2013;62:610-616
27. Gooneratne NS, Weaver TE, Cater JR, Pack FM, Arner HM, Greenberg AS, Pack AI. Functional outcomes of excessive daytime sleepiness in older adults. *J Am Geriatr Soc.* 2003;51:642-649
28. Eijsvogel MM, Wiegersma S, Randerath W, Verbraecken J, Wegter-Hilbers E, van der Palen J. Obstructive sleep apnea syndrome in company workers: Development of a two-step screening strategy with a new questionnaire. *J Clin Sleep Med.* 2016;12:555-564
29. Pataka A, Daskalopoulou E, Kalamaras G, Fekete Passa K, Argyropoulou P. Evaluation of five different questionnaires for assessing sleep apnea syndrome in a sleep clinic. *Sleep Med.* 2014;15:776-781

30. Netzer N, Riccardo A, Netzer C, Clark K, Strohl K. Using the berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999;131:485-491
31. Seet E, Chung F. Management of sleep apnea in adults - functional algorithms for the perioperative period: Continuing professional development. *Can J Anaesth.* 2010;57:849-864
32. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. Validation of the berlin questionnaire and american society of anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. *Anesthesiology.* 2008;108:822-830
33. Tantrakul V, Sirijanchune P, Panburana P, Pengjam J, Suwansathit W, Boonsarngsuk V, Guilleminault C. Screening of obstructive sleep apnea during pregnancy: Differences in predictive values of questionnaires across trimesters. *J Clin Sleep Med.* 2015;11:157-163
34. Cass AR, Alonso WJ, Islam J, Weller SC. Risk of obstructive sleep apnea in patients with type 2 diabetes mellitus. *Fam Med.* 2013;45:492-500
35. Olszewski K, Wolf D. Obstructive sleep apnea among commercial motor vehicle drivers: Using evidence-based practice to identify risk factors. *Workplace Health Saf.* 2013;61:479-485
36. Burks SV, Anderson JE, Bombyk M, Haider R, Ganzhorn D, Jiao X, Lewis C, Lexvold A, Liu H, Ning J, Toll A, Hickman JS, Mabry E, Berger M, Malhotra A, Czeisler CA, Kales SN. Nonadherence with employer-mandated sleep apnea treatment and increased risk of serious truck crashes. *Sleep.* 2016;39:967-975
37. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, Tracy RP, Rueschman M, Blumenthal RS, Lewis EF, Bhatt DL, Redline S. Cpap versus oxygen in obstructive sleep apnea. *N Engl J Med.* 2014;370:2276-2285
38. Shah N, Hanna DB, Teng Y, Sotres-Alvarez D, Hall M, Loreda JS, Zee P, Kim M, Yaggi HK, Redline S, Kaplan RC. Sex-specific prediction models for sleep apnea from the hispanic community health study/study of latinos. *Chest.* 2016
39. Chai-Coetzer CL, Antic NA, Rowland LS, Catcheside PG, Esterman A, Reed RL, Williams H, Dunn S, McEvoy RD. A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care. *Thorax.* 2011;66:213-219
40. Neal B, MacMahon S, Chapman N. Effects of ace inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomised trials. Blood pressure lowering treatment trialists' collaboration. *Lancet.* 2000;356:1955-1964
41. Roca GQ, Redline S, Claggett B, Bello N, Ballantyne CM, Solomon SD, Shah AM. Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community-dwelling cohort: The atherosclerosis risk in communities-sleep heart health study. *Circulation.* 2015;132:1329-1337