Title: Diagnostic accuracy of home sleep apnea testing using peripheral arterial tonometry for sleep apnea syndrome: protocol for a systematic review and meta-analysis

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Masahiro Ichikawa is the guarantor. Masahiro Ichikawa drafted the manuscript.

All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. Masahiro Ichikawa developed the search strategy. All authors read, provided feedback and approved the final manuscript.

funding: fundamental research funding of Yokohama City University (award/grant number N/A)

**INTRODUCTION**

**Rationale**

Obstructive sleep apnea (OSA) is common, and may affect approximately 1 billion adults aged 30-69 years worldwide. Of these, an estimated 425 million suffer from moderate or severe disease (1). Evidence has suggested OSA is associated with an increased incidence of hypertension, type 2 diabetes, coronary artery disease, and stroke, and early diagnosis is important to prevent these complications. The gold standard for diagnosing OSA is in-laboratory polysomnography (PSG). However, PSG is expensive, labor intensive, limited in available facilities, and can result in long waiting times(2, 3). The home sleep apnea testing (HSAT) has been developed to solve these problems. The American Academy of Sleep medicine (AASM) guidelines recommend HSAT with at least nasal pressure, chest and abdominal respiratory inductance plethysmography, and oximetry or peripheral arterial tonometry (PAT) with oximetry and actigraphy (4). Sleep studies are classified as Type I-IV, with Type Ⅲ recording two respiratory variables, oxygen saturation, and one cardiac variable. (4) A meta-analysis of HSAT suggested that HSAT alone could not be the gold standard test for OSA due to the low sensitivity and specificity. However, the meta-analysis did not include studies that uses HSAT with PAT (5). Watch-peripheral arterial tone (WatchPAT), one of the HSATs, is a device that uses PAT can be worn like a wristwatch and continuously records PAT, heart rate, oxygen saturation, and actigraphy at night. PAT signals are measured continuously in the peripheral arterial bed of the fingertip. WatchPAT can indirectly detect apneic/hypopneic events by monitoring PAT because PAT reflects physiological changes in pulsatile arterial volume that are modulated by sympathetic nerve activity (6). While other HSAT cannot accurately measure total sleep time, WatchPAT can accurately measure actual total sleep time (7), which may increase sensitivity. WatchPAT is simple and can be an alternative diagnostic tool to PSG if it has sufficient diagnostic accuracy. Furthermore, NightOwl is another HSAT that uses PAT(8). This review will investigate the diagnostic accuracy of HSAT using PAT and determine whether HSAT using PAT are replaceable for PSG.

**OBJECTIVE**

This systematic review and meta-analysis aims to evaluate the diagnostic accuracy of HSAT using PAT for OSA among patients suspected of having OSA and to determine if PSG can be replaced by HSAT using PAT. Secondary objective is whether HSAT using PAT can classify the severity of OSA according to AASM guideline.

**METHODS**

We will follow the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) statement (9).

**Criteria for considering this review**

**Types of studies**

We will include all studies on the diagnostic accuracy of HSAT using PAT for evaluating OSA. We will include the studies designed as follows: prospective or retrospective observational (cohort or cross-sectional) studies, secondary analysis of randomized controlled trials (RCTs), and diagnostic case-control studies. We will not exclude studies based on language, countries, year of publication, or publication status. We will exclude case series, case reports, case control study of two-gate design, reviews, editorials, or studies for which the true positive, true negative, false positive, and false negative cannot be calculated.

**Participants**

The target participants are patients suspected of having OSA based on medical and sleep history, and physical examination.

**Target condition**

The target condition is OSA.

**Setting**

We expect studies conducted in outpatient settings; however, we will accept any type of settings.

**Index tests**

The index test assessed in this review is HSAT using PAT. The findings are generally categorized as Mild OSA (AHI 5 to 14.9), moderate OSA (AHI 15 to 29.9), and severe OSA (AHI 30 or more) (10). Our primary interest is whether AHI of 5 or more determined by HSAT using PAT can diagnose mild or more severe OSA accurately, as compared with PSG. We also investigate if HSAT using PAT can classify the severity of OSA according to AASM guideline. We will also include other positive findings of each imaging modality as the authors defined. We will allow the judgment of these positive findings by any physicians in included studies.

**Reference standard**

The reference standard is in-laboratory PSG. For the severity using AHI, we will use the same definition as HSAT using PAT.

**Search methods for identification of studies**

**Electronic searches**

We will conduct a literature search to identify all published and unpublished eligible studies. We will translate non-English articles and thoroughly assess them for potential inclusion as necessary. We will search in the following electronic databases: MEDLINE via Pubmed, EMBASE via ProQuest Dialog, and Cochrane Central Register of Controlled Trials (CENTRAL). We will also search for the World Health Organization international clinical trials Platform Search Portal (ICTRP) and ClinicalTrials.gov to find ongoing and unpublished studies. We will check the reference lists of studies, including international guidelines as well as the reference lists of eligible studies and articles citing eligible studies.

**Data collection and analysis**

**Selection of studies**

The two independent reviewers (MI and TA) will screen the results of the search according to our search strategy, with initial title and abstract screening followed by full-text screening. If two reviewers disagree, they will discuss to resolve the disagreement or consult with a third reviewer. We will contact original authors via e-mail if relevant data is missing.

**Data extraction and management**

Two independent reviewers (MI and TA) will conduct independent data extraction of the included studies using sheet including the following information.

The sheet includes the information on the first author’s name, year of publication, country, study design, sample size, setting, participant’s demographic data (mean age and body mass index, sex and comorbidity), participant’s inclusion and exclusion criteria and information of index tests and reference standard. We will calculate true positives, false positives, true negatives, and false negatives from 2×2 table. When only receiver operating characteristic curves were reported, WebPlotDigitizer 4.4 was used to extract sensitivity and specificity information (11).

**Assessment of methodological quality**

Two independent reviewers (MI and TA) will independently assess the risk of bias and applicability using the QUADAS-2 tool (12). We will revise the signaling questions in the QUADAS-2 according to this review question.

**Statistical analysis and data synthesis**

We will compare the results of HSAT using PAT to that of the reference standard. We will extract data for 2×2 tables of HSAT using PAT against the reference standard from each study. We will present a summary of findings table. We will show estimates of sensitivity and specificity with 95% confidence intervals (CI) of HSAT using PAT per study using forest plots.

We will conduct estimates of the accuracy of each study using a scatter plot in a receiver operating characteristic (ROC). We will conduct a meta-analysis for HSAT using PAT. In the meta-analysis, we will use a bivariate model to report the summary point estimate of sensitivity and specificity with 95% CI. For better interpretation of our result, we will also tabulate the number of false negatives and false positives when low-, moderate-, and high-prevalence of OSA are applied to the pooled sensitivity and specificity. We will perform all analyses using Stata version 16.1 for Windows (Stata Corporation, College Station, TX, USA) and Review Manager 5.4.1 (Cochrane Collaboration, London, United Kingdom).

**Investigations of heterogeneity**

Whenever possible, we will conduct subgroup analyses on the following groups. 1. Type of inspection location (home versus laboratory) (5) 2. Type of patients (patients with significant comorbidities as defined by AASM guideline versus patients without significant comorbidities (4) 3. Type of risk of OSA (patients with signs suggestive of moderate to severe OSA as defined by AASM guideline (4) versus patients without signs). 4. Type of the definition of a hypopnea event (Changes in flow associated with 3% oxygen deprivation or cortical arousal versus Changes in flow associated with 4% oxygen deprivation without considering cortical arousal (4) or the author’s own definition). 5. Type of index test. To examine the subgroup differences, we will perform a meta-regression, and present the relative diagnostic odds ratios and the 95% confidence intervals. If the number of studies is limited and the above analysis is not possible, we will present each SROC curve for each subgroup and qualitatively assess the heterogeneity.

**Sensitivity analysis**

We will assess the robustness to explore diagnostic accuracy for HSAT using PAT by excluding studies judged to be at high risk of bias in the domains of index test or reference standard in QUADAS-2 assessment.

**Appendix 1: MEDLINE (via PubMed) search strategy**

#1 "peripheral arterial tone"[tiab]

#2 "peripheral arterial tonometry"[tiab]

#3 "watchpat"[tiab]

#4 “nightowl”[tiab]

#5 “PAT”[tiab]

#6 "Pulse Arterial Tonometry"[tiab]

#7 “wearable electronic devices”[Mesh]

#8 “wearable electronic devices”[tiab]

#9 “portable monitoring”[tiab]

#10 “HSAT”[tiab]

#11 “home sleep apnea testing”[tiab]

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 "Sleep Apnea Syndromes"[Mesh]

#14 “snoring”[Mesh]

#15 “snoring”[tiab]

#16 “sleep”[tiab] AND (“apnoea”[tiab] OR “apnea”[tiab])

#17 “hypopnea”[tiab] OR “hypopnoea”[tiab]

#18 “OSA”[tiab]

#19 “SHS”[tiab]

#20 “OSAHS”[tiab]

#21 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22 #12 AND #21

#23 “animals”[Mesh] NOT “humans”[Mesh]

#24 #22 NOT #23

**Appendix 2: CENTRAL search strategy**

#1 "peripheral arterial tone":ti,ab

#2 "peripheral arterial tonometry":ti,ab

#3 watchpat:ti,ab

#4 nightowl:ti,ab

#5 PAT:ti,ab

#6 "Pulse Arterial Tonometry":ti,ab

#7 [mh "wearable electronic devices"]

#8 "wearable electronic devices":ti,ab

#9 "portable monitoring":ti,ab

#10 HSAT:ti,ab

#11 "home sleep apnea testing":ti,ab

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 [mh "SleepApneaSyndromes"]

#14 [mh snoring]

#15 snoring:ti,ab

#16 sleep:ti,ab AND (apnoea:ti,ab OR apnea:ti,ab)

#17 hypopnea:ti,ab OR hypopnoea:ti,ab

#18 OSA:ti,ab

#19 SHS:ti,ab

#20 OSAHS:ti,ab

#21 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22 #12 AND #21

#23 [mh animals] NOT [mh humans]

#24 #22 NOT #23

**Appendix 3: EMBASE (via ProQuest Dialog) search strategy**

#1 ab( "peripheral arterial tone") OR ti( "peripheral arterial tone")

#2 ab("peripheral arterial tonometry") OR ti("peripheral arterial tonometry")

#3 ab("watchpat") OR ti("watchpat")

#4 ab(“nightowl”) OR ti(“nightowl”)

#5 ab(“PAT”) OR ti(“PAT”)

#6 ab("Pulse Arterial Tonometry") OR ti("Pulse Arterial Tonometry")

#7 EMB.EXACT.EXPLODE(“wearable device”) OR EMB.EXACT.EXPLODE(“wearable computer”)

#8 ab(“wearable electronic devices”) OR ti(“wearable electronic devices”)

#9 ab(“portable monitoring") OR ti(“portable monitoring")

#10 ab(“HSAT") OR ti(“HSAT")

#11 ab(“home sleep apenea testing") OR ti(“home sleep apnea testing")

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 EMB.EXACT.EXPLODE("sleep apnea syndrome")

#14 EMB.EXACT.EXPLODE("snoring")

#15 ab("snoring") OR ti("snoring")

#16 ab(“sleep” AND (“apnoea” OR “apnea”)) OR ti(“sleep” AND (“apnoea” OR “apnea”))

#17 ab(“hypopnea” OR “hypopnoea”) OR ti(“hypopnea” OR “hypopnoea”)

#18 ab("OSA") OR ti("OSA")

#19 ab("SHS") OR ti("SHS")

#20 ab("OSAHS") OR ti("OSAHS")

#21 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

#22 #12 AND #21

#23 EMB.EXACT.EXPLODE(“animal”) NOT EMB.EXACT.EXPLODE(“human”)

#24 #22 NOT #23

**Appendix 4: ICTRP search strategy**

(“sleep apnea syndrome” OR “OSA” OR “SHS” OR “hypopnea” OR “snoring”)

AND

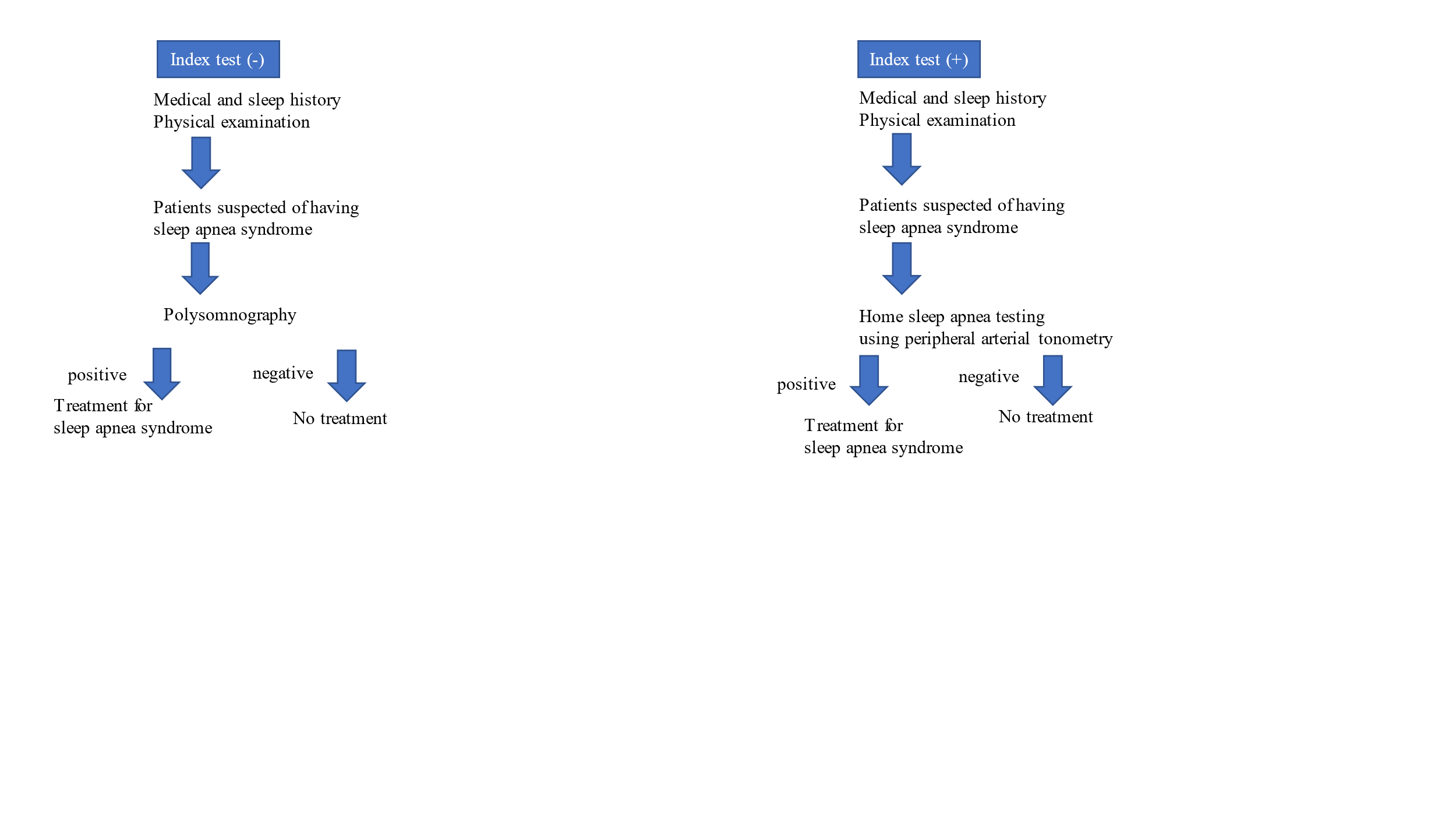
(“peripheral arterial tone” OR “peripheral arterial tonometry” OR “watchPAT” OR “nightowl” OR “portable monitoring” OR “HSAT”)

**Appendix 5: ClinicalTrials.gov search strategy**

Condition or disease: sleep apnea syndrome OR OSA OR SHS OR hypopnea OR snoring

Intervention: peripheral arterial tone OR peripheral arterial tonometry OR watchPAT OR nightowl OR portable monitoring OR HSAT

**Appendix 6: Clinical pathway for this review question**



**REFERENCES**

1. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. The Lancet Respiratory Medicine. 2019;7(8):687-98.

2. Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. Access to Diagnosis and Treatment of Patients with Suspected Sleep Apnea. American journal of respiratory and critical care medicine. 2004;169(6):668-72.

3. Shinoda M, Yamakawa T, Takahashi K, Nagakura J, Suzuki JS, 2019 #392}, Sakamoto R, et al. PREVALENCE OF OBSTRUCTIVE SLEEP APNEA DETERMINED BY THE WATCHPAT IN NONOBESE JAPANESE PATIENTS WITH POOR GLUCOSE CONTROL AND TYPE 2 DIABETES. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2019;25(2):170-7.

4. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. Journal of Clinical Sleep Medicine. 2017;13(03):479-504.

5. El Shayeb M, Topfer L-A, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. Canadian Medical Association Journal. 2014;186(1):E25-E51.

6. 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 Studiesa. Chest. 2003;123(3):695-703.

7. Pillar G, Berall M, Berry R, Etzioni T, Shrater N, Hwang D, et al. Detecting central sleep apnea in adult patients using WatchPAT—a multicenter validation study. Sleep and Breathing. 2020;24(1):387-98.

8. Massie F, De Almeida DM, Dreesen P, Thijs I, Vranken J, Klerkx S. An evaluation of the Night Owl home sleep apnea testing system. Journal of Clinical Sleep Medicine. 2018;14(10):1791-6.

9. Salameh J-P, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, Macaskill P, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ. 2020:m2632.

10. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea. JAMA. 2020;323(14):1389.

11. Rohatgi A. WebPlotDigitizer. Website: https://automeris.io/WebPlotDigitizer

Version: 4.5.

12. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.