Taylor & Francis
Taylor & Francis Group

Expert Review of Molecular Diagnostics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iero20

Current and future strategies for diagnostic and management of obstructive sleep apnea

Sartaj Khurana, Narshone Soda, Muhammad J. A. Shiddiky, Ranu Nayak & Sudeep Bose

To cite this article: Sartaj Khurana, Narshone Soda, Muhammad J. A. Shiddiky, Ranu Nayak & Sudeep Bose (2021) Current and future strategies for diagnostic and management of obstructive sleep apnea, Expert Review of Molecular Diagnostics, 21:12, 1287-1301, DOI: 10.1080/14737159.2021.2002686

To link to this article: https://doi.org/10.1080/14737159.2021.2002686

Published online: 24 Nov 2021.

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
2021, VOL. 21, NO. 12, 1287–1301
https://doi.org/10.1080/14737159.2021.2002686

Taylor & Francis
Taylor & Francis Group

Current and future strategies for diagnostic and management of obstructive sleep apnea

Sartaj Khurana[a,b], Narshone Soda[c], Muhammad J. A. Shiddiky[c], Ranu Nayak[d] and Sudeep Bose[a,b]

[a]Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, India; [b]Amity Institute of Molecular Medicine and Stem Cell Research, Amity University Uttar Pradesh, Noida, India; [c]Queensland Micro- and Nanotechnology Centre (Qmnc) and School of Environment and Science (ESC), Griffith University, Brisbane, Australia; [d]Amity Institute of Nanotechnology, Amity University Uttar Pradesh, Noida, India

ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is a common sleep disorder with multiple comorbidities including hypertension, diabetes, and cardiovascular disorders. Detected based on an overnight sleep study is called polysomnography (PSG); OSA still remains undiagnosed in majority of the population mainly attributed to lack of awareness. To overcome the limitations posed by PSG such as patient discomfort and overnight hospitalization, newer technologies are being explored. In addition, challenges associated with current management of OSA using continuous positive airway pressure (CPAP), etc. presents several pitfalls.

Areas Covered: Conventional and modern detection/management techniques including PSG, CPAP, smart wearable/pillows, bio-motion sensors, *etc.,* have both pros and cons. To fulfill the limitations in OSA diagnostics, there is an imperative need for new technology for screening of symptomatic and more importantly asymptomatic OSA patients to reduce the risk of several associated life-threatening comorbidities. In this line, molecular marker-based diagnostics have shown great promises.

Expert Opinion: A detailed overview is presented on the OSA management and diagnostic approaches and recent advances in the molecular screening methods. The potentials of biomarker-based detection and its limitations are also portrayed and a comparison between the standard, current modern approaches, and promising futuristic technologies for OSA diagnostics and management is set forth.

ABBREVIATIONS AHI: Apnea hypopnea index; AI: artificial intelligence; CAM: Cell adhesion molecules; CPAP: Continuous Positive Airway Pressure; COVID-19: Coronavirus Disease 2019; CVD: Cardiovascular disease; ELISA: Enzyme linked immunosorbent assay; HSAT: Home sleep apnea testing; IR-UWB: Impulse radio-ultra wideband; MMA: maxillomandibular advancement; PSG: Polysomnography; OSA: Obstructive sleep apnea; SOD: Superoxide dismutase; QD: Quantum dot

ARTICLE HISTORY
Received 4 May 2021
Accepted 2 November 2021

KEYWORDS
Biosensor; molecular marker; OSA; OSA comorbidities; OSA management; polysomnography; RNA based detection; smart detection; smart wearables

1. Introduction

Obstructive sleep apnea (OSA) is the most common forms of sleep disordered breathing recognized by a repeated occurrence of upper airway obstruction and is usually linked with oxygen depletion and unusual pauses in the breathing pattern during the course of sleep [1,2]. OSA cases have been steeply rising globally as recently reported in *The Lancet Respiratory Medicine* [3]. Unfortunately, the onset of OSA is concordantly associated with several ailments, such as cardiovascular disorders, memory loss, depression, hypertension, *etc* [4–7]. In fact, OSA has been a causative factor for more than 38,000 cardiovascular deaths worldwide annually and 30–70% of sufferers are diagnosed with hypertension [8]. More than 60% of the stroke patients have difficulty in breathing during sleep [9]. Heightened airway obstruction during sleep, leading to OSA, has been observed to affect about ~2% to 4% of children between 2 and 8 years old [10]. OSA in children may affect brain health as childhood OSA has been shown to be associated with the lowering of intelligence quotient causing neurological dysfunction as corroborated by different studies [11]. Sleep disordered breathing in 5-year-old children caused impairment of memory and general intelligence, as reported by Gottlieb and team [12]. Pediatric OSA is primarily due to obesity and adenotonsillar hypertrophy (enlarged tonsils) and is diagnosed initially with the help of a physical examination of the neck, mouth, tongue, and adenoids followed by a polysomnogram if necessary. Therefore, adenotonsillectomy is the first line of treatment preferred for pediatric OSA, unlike CPAP, which is only recommended if OSA persists even after the surgery [13,14]. In elderly people with OSA, diagnosis is made using polysomnography; however, underdiagnosis in elderly patients is more common than younger patients [15], whereas CPAP is the preferred mode of treatment as it improves breathing, quality of life, OSA-related symptoms, symptoms of depression, as well as neurocognitive aspects; however, its effects are still controversial as majority of the data pertains to middle aged adults [16,17]. In comparison to children and older adults, the prevalence of OSA is more

CONTACT Sudeep Bose sbose1@amity.edu Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, UP 201301, India; Amity Institute of Molecular Medicine and Stem Cell Research, Amity University Uttar Pradesh, Noida, Up 201301, India; Ranu Nayak rnayak@amity.edu Amity Institute of Nanotechnology, Amity University Uttar Pradesh, Noida, UP 201301, India

prominent in middle aged people, who are screened using structured questionnaires and physical examination followed by diagnosis using polysomnography. Once diagnosed, different treatment strategies such as lifestyle changes, CPAP therapy, oral appliances, positional therapy, *etc*., are advised [18].

OSA is majorly associated with comorbid conditions such as hypertension, CVD, diabetes, *etc*. Severe OSA is an independent risk factor for hypertension as subjects with severe OSA exhibit increased likelihood of becoming hypertensive than the general population as corroborated by the Wisconsin Sleep Cohort Study [19]. Moreover, OSA severity has been found to be positively correlated with coronary atherosclerotic plaque volume suggesting the onset of cardiovascular diseases in OSA subjects [20]. Literature also cites that the incidence of OSA is considerably higher in patients with AF (32–49%) suggestive of the potential of OSA as a probable causative factor for AF manifestation [21,22]. Furthermore, the likelihood of developing diabetes in patients with OSA is high and with progressing severity, this likelihood of T2DM development also increases [23]. OSA associated intermittent hypoxia which is attributed to sleep deprivation impairs insulin sensitivity, glucose effectiveness, insulin secretion, and pancreatic β-cell function [24,25].

An effective remedy to the hidden struggle of OSA patients can be accomplished by providing more awareness, improved disease management, and more importantly by developing easy, portable screening tools that eliminates the need for skilled healthcare personnel. Simple home test kits/devices where a patient can self-test to diagnose and also monitor the severity of the disease can tremendously improve human lifestyle and overall health. Currently, OSA is managed with continuous positive airway pressure (CPAP), which allows the patients to breathe normally while sleeping. Apart from CPAP, doctors prescribe natural methods such as weight loss or surgical methods as appropriate.

OSA is usually diagnosed based on an overnight sleep study known as polysomnography, which entails the monitoring of essential parameters such as heart rate, muscle movements, limb movements, eye movements, blood oxygen levels, body posture, respiratory efforts, breathing patterns including absences or pauses, and snoring or other sounds. However, due to certain downsides of the technique, such as tediousness and patient discomfort, as well as the patient unawareness, the prevalence is under reported. To overcome this, OSA patients have recently been opting for home sleep apnea testing due to its convenience [26].

The continuous rise in prevalence of OSA in different populations across the globe raises an alarmingly important concern. In spite of the acute seriousness of this disease, common people tend to take this disease lightly or most often ignore. Patients also feel ashamed to seek medical help so as to avoid revealing their snoring habit. Thus, there is urgent need for the development of portable and facile detection methods for OSA. Recent reviews have elaborated on the currently available techniques for OSA detection and treatment including CPAP, ECG-based detection, smart pillows, telemonitoring, and sensors. However, their drawbacks such as affordability, timing, and calculation of sleep apneic events during sleep limit their usage [27–29]. Additionally, new techniques such as the electric nose detects OSA with high accuracy by detecting the volatile organic compound (VOC) shift in pharyngeal liquid, and breath condensates between OSA patients and healthy subjects [30]. Electric nose technology is a promising noninvasive and cost-effective technology that profiles VOCs in the exhaled breath for diagnosis [31]. OSA patients exhibit higher levels of Fractional Exhaled Nitric Oxide (FeNO) as compared to non-OSA individuals. Therefore, exhaled breath analysis by electric nose technologies could prove to be a promising strategy in detecting OSA and understanding the underlying molecular mechanisms [32,33].

Growing literature has shed some light on the accuracy and utility of modern detection and management strategies such as smart wearables, bio-motion sensors, *etc*. These strategies have demonstrated promising results and exhibited their caliber as new-age detection methods [34].

Literature survey indicates that there are several review articles on OSA till date that have explained about the conventional and few modern OSA detection methods such as physical screening, PSG and home sleep apnea testing; also, on management of the disease based on CPAP and life style management. However, no evidence has surfaced till date emphasizing a comparative analysis between the traditional methods vs modern and futuristic detection methods. A collective and pooled piece of information pertaining to the in-depth comparison between polysomnography and newer detection methods such as smart wearables, biomotion sensors, facial photography, artificial intelligence, *etc*. and their technical advantages over the current polysomnographic analysis and the very promising molecular marker-based diagnostics is warranted to bridge the existing gaps in knowledge. We have also provided a comprehensive overview on the various ways of OSA management and their implications as well as modern detection technologies that are either available commercially or yet in the research and development phase. Furthermore, we highlight on the potential futuristic diagnostic tools/methods that can bring about the dream-come-true portable home use test kits/devices for OSA patients. In this context, we bring in acquaintance to novel biomarkers that can favorably detect OSA in its molecular level and most likely during the onset of the disease. A perspective is presented toward the development of biosensors that can detect the potential OSA biomarkers and their related comorbidities. Herein, the linked benefits and challenges are also discussed herewith. Toward this goal, this review highlights the evident differences between the standard and the state-of-the-art methods of detection and management of OSA and elaborating on their potential as the future of diagnostics in sleep medicine.

2. Screening and detection of OSA

2.1. Physical screening

The growing socio-economic burden of OSA and its importance in morbidity and mortality has led to the development of several screening tools. These screening tools include questionnaires like Berlin, STOP, STOP-BANG, Epworth Sleeping Scale, *etc*. The Stop and STOP-BANG questionnaires comprise

of self-answering questions that assess **s**noring, **t**iredness, **o**bserved apneas and high blood **p**ressure, whereas the BANG section assesses **B**MI, **a**ge, **n**eck circumference and male **g**ender. STOP-BANG has been observed to demonstrate the a sensitivity of 96% in patients with polysomnographically proven moderate-to-severe OSA with increasing sensitivity based on the progressing severity; however, its specificity is reported to be the lowest compared to the other tools [35]. The Berlin questionnaire (BQ) was developed in 1999 and encompasses three sections about snoring, daytime fatigue with sleepiness and medical history and anthropometric measures respectively. The sensitivity and specificity of BQ has been reported to be 97.3% and 91.7%, respectively, moderate-to-severe categories of OSA [36]. Another crucial screening tool is the Epworth Sleeping Scale (ESS) that assesses the presence of OSA based on daytime sleepiness. The highest ESS sensitivity and specificity was observed to be 46.1% to 79.9% (AHI ≥ 30) and 75% (mild OSA), respectively [36].

2.2. Conventional method: polysomnography

The initial screening procedure of OSA patients usually starts with the assessment of their sleep history in order to identify symptoms, risk factors, and followed by a physical examination. Physical examination such as neck circumference, body mass index, tongue position, and craniofacial features can indicate the presence of OSA [37]. Following the recordings of the physical examination, patients are referred for polysomnography (PSG), an overnight sleep study which is the gold standard test for diagnosis of OSA.

A routine polysomnogram involves an extensive monitoring and recording of sleep stages, limb movements, airflow, respiratory effort, heart rate, body position, and blood levels of saturated oxygen. This study is performed under the supervision of a qualified sleep technician in a dedicated sleep laboratory. While the patient sleeps, these parameters are monitored with the help of the following studies- (i) electroencephalogram; (ii) electrocardiogram, (iii) electro-oculogram (iv) electromyogram, (v) airflow movement, (vi) pulse oximetry, and (vii) body position. Electroencephalogram involves the recording of the electrical activity on the surface of the brain. Polysomnogram records only a limited electroencephalographic data to only ensure efficient identification of sleep and wakefulness stages. Electro-oculogram is aimed at monitoring and recording the changes occurring in the eye movements during sleep and wakefulness, and any fluctuation in the signal is recorded as a deflection. Electromyogram is an electrodiagnostic medicine technique aimed at evaluating and recording the electrical activity produced by muscles of the head, neck, and legs. Airflow movement is measured using the nasal pressure sensor, which accurately detects the nocturnal respiratory events. Cardiac rhythm is monitored using an electrograph that evaluates the nocturnal average heart rate, highest heart rate along with cardiac arrhythmias. Pulse oximetry is performed to determine the oxygen saturation of arterial blood, and lastly, body position is monitored because snoring and upper airway obstruction during sleep are influenced by gravity [38,39]. Despite being the gold standard for OSA diagnosis, PSG has its own limitations including long wait time (3 to 11 months) for appointments, poor sleep efficiency, and patient discomfort and night-to-night variability. Moreover, a skilled sleep technician is continuously needed for ensuring successful completion of optimal data recording, and PSG might be inadequate to demonstrate a patient's vulnerability to the overall consequences of OSA [40].

2.3. Home sleep apnea testing

Home sleep apnea testing (HSAT) is aimed at self-diagnosis of OSA and is being currently used by OSA patients. It monitors parameters such as airflow and oximetry but does not record the sleep patterns. Due to the longer waiting times for PSG analysis in the hospitals, portable monitoring, and HSAT systems have been developed. Technological advancements in HSAT have revolutionized the face of sleep medicine. Vivos Therapeutics Inc. have recently developed a wearable-based home sleep apnea test called VivoScore that comprises of a ring-based sensor connected to a smart phone application and evaluates the sleep quality and detects sleep apnea. VivoScore uses a single sensor ring that is worn by the patient on the finger and is connected *via* Bluetooth to a mobile phone for data capture. VivoScore is simpler to use and more cost-effective compared to the existing HSAT. Considering the sensitivity (approximately 80%) of the HSAT technique as well as the convenience of OSA diagnosis (at patient's home), it still has certain drawbacks such as under estimation of severity of sleep-related breathing disorders like OSA. Moreover, a negative or inconclusive result of home sleep apnea testing still requires a polysomnographic analysis to ensure the absence of OSA in the patient. Furthermore, home sleep apnea tests are unable to record sleep and only monitor the frequency of the disordered breathing events. Additionally, sensor failure during the night may result in false readings that may lack usefulness and require further testing. Moreover, due to difference in the sensors between various portable monitors, it is difficult to draw a comparison between the readings. Lastly, the interpersonal night-to-night variability is a major challenge that impacts the accuracy of the OSA severity [26].

3. Modern detection methods

The sleep medicine field has been advancing at a great pace due to the rising cases of sleep-related disorders. There is a pressing need for developing accurate and reliable diagnostic criteria to ensure appropriate treatment [41]. Considering the limitations of PSG, like patient discomfort, non-contact devices such as an impulse radio ultra-wide band radar has been developed for the diagnosis of OSA [42–44].

3.1. Wearable devices

Wearable devices such as smart watches, wristbands, and rings have garnered a lot of attention both in research as well as industry with a wide range of benefits including early detection, determining the correlations with lifestyle and health, and remote supervision of health. *HealthGear* is one such wearable real-time system comprising of a set of

physiological sensors connected wirelessly via Bluetooth to a smart phone. *HealthGear* has proven to be effective in monitoring sleep patterns, thereby diagnosing sleep apnea events by monitoring the pulse and blood oxygen levels. This device has advantages such as light weight and wireless, real-time analysis, remote access by the sleep specialist, and ease of use [45]. ScanWatch was unveiled in 2020 and is claimed to be "the world's first clinically validated hybrid smartwatch capable of detecting risks of arrhythmia and sleep apnea." However, the approval from the FDA is still pending. Other smart wearables like Amazfit ZenBuds possess sleep tracking features that analyze the sleep quality and sleep stage information, monitored, and reported *via* a smartphone application. Moreover, the potential of wrist-worn reflective photoplethysmography (rPPG) as an effective AHI estimation method in comparison to the reference method (PSG) has been elaborate recently. Findings from Papini *et al.* suggested that the measurements from wrist-worn rPPG were similar to the gold standard polysomnography analysis and concluded that rPPG measurements can be incorporated in smart watches and alike, for OSA diagnosis [46]. Another similar study developed a developed a nasal wearable based on PPG that detects apnea episodes from breathing patterns [47]. Another piece of evidence proposed a method of OSA detection based on the use of sensors and wristbands capable of monitoring the diaphragm movement and detecting the apnea [48]. Some of these non-intrusive wearables are also capable of recording and analyzing the patients' ECG for classification of OSA, thereby achieving an accuracy of 83% [49]. Furthermore, to ensure convenient monitoring of OSA, wearable patches have been developed that have the potential to track the patients' breathing pattern with the help of bioimpedance and machine learning algorithms. This approach, as corroborated by the researchers at Ghent University, had an accuracy of 73% at detecting OSA events [50]. Also, latest versions of smart-watches from Iconic manufacturers such as Garmin, Fitbit, Apple, Samsung, Mio, Withings, *etc.,* have achieved an accuracy of 90% in diagnosing sleep patterns and OSA. Smart wearables like headbands and eye-masks possess advanced technology of monitoring brain activity and eye movements. The Vivosmart 4 from Garmin employs advanced sleep tracking monitors blood oxygen levels during sleep using a built-in oximetry mode. Fitbit offers its wearers sleep readings and oxygen levels using its heart rate sensors and its algorithms. Other sleep trackers like BioStrap EVO, Go2Sleep from SleepOn, Beddit, and others are readily available in the market and are effective in detecting the sleep patterns. Bed sensors underneath the mattresses have gained attention as they are capable of detecting body movements, sleep patterns, breathing patterns and even cardiac activities [51]. However, such sleep trackers also have a few limitations such as: (i) they are expensive, (ii) they are not compatible with third party applications, (iii) heart rate monitor is not always consistent, (iv) interface is difficult to read, (v) non-returnable in some cases, *etc*. Further thorough research and in-depth investigations are still needed in these arenas to commercialize such futuristic methods and ensure their availability to the common man.

3.2. Bio-motion sensors

Non-contact biomotion sensors have been used for quite a few years for identifying sleep–wake patterns in humans. Bio-motion sensors function *via* ultra-low power reflected radio frequency waves that detect the subject's sleep movements. Some studies have reported an overall accuracy of the sensor to be 87.3% [52]. The most well-known biomotion sensor that has been widely used for OSA detection is *SleepMinder* by BiancaMed Ltd., which assesses the breathing pattern and detects the severity of OSA. Recent use of the *SleepMinder* has illustrated its accuracy as more than 90% in detecting moderate to severe OSA as compared to the laboratory specific polysomnography. Also, the *SleepMinder* is capable of detecting the AHI as precisely as 91% with a sensitivity and specificity of 89% and 92%, respectively [53]. However, the performance of the device is reported to be inferior in females than males attributed to gender differences such as differences in the body physique [54].

3.3. Radio wave-based detection

Systems based on radio waves detect the breathing patterns of the OSA subjects based on the difference in chest movements that differentiate the normal breathing pattern with the intermittent breathing during apneic episodes. A non-invasive detection system using C-Band wireless sensing made use of a wireless transmitter and receiver operator of 4.8 GHz frequency that is effective at detecting OSA based on the above mentioned breathing patterns [55]. An impulse radio-ultra wideband (IR-UWB) radar sensor has been developed that is capable of monitoring and measuring body movements from limb movements to respiratory changes. The sensor is able to accurately detect respiratory events during sleep without contact [56]. These techniques are advantageous over the currently used PSG in terms of non-intrusiveness, flexibility, and cost-effectiveness.

3.4. Piezo sensors

To overcome the challenges posed by PSG, studies have been attempted to diagnose OSA based on investigation of snoring sounds using piezoelectric sensors [57]. These sensors are capable of detecting snoring, episodes of respiratory events and heartbeats, and eventually differentiate disordered breathing from normal breathing. The vibrations in the neck caused by snoring as well as pulse rates are also detected by the sensor. The accuracy of piezoelectric sensors has been observed to be more than 70% [58]. Piezoelectric sensors make use of an algorithm that allows prompt sleep–wake detection. Based on the pre-set apnea index and sleep duration, the sensor classifies the patients as above or below AHI of 15. While some studies have achieved a sensitivity of 88% in patients with severe OSA [59], others have claimed a sensitivity as high as 90% in patients with medium intensity snoring

Table 1. Conventional vs modern methods of detection of OSA.

Type of Detection	Method	Duration	Specificity	Accuracy	Efficacy	Sensitivity	Cost (USD)
Conventional	Polysomnography	8 hours	97%	NA	NA	75% – 88%	600–5,000
	Home sleep apnea testing	8 hours	25% – 100%	92%	NA	77%-96%	4516
Modern	Wearables Devices	8 hours	88%	78%	NA	83% – 90%	100–800
	Biomotion sensors	3–6 hours	76%	83%	NA	87% – 89%	Under R&D stage
	Radio-wave based detection	3–6 hours	84%-100%	74%-100%	NA	93% – 100%	Under R&D stage
	Piezo sensors	3–6 hours	74%-85%	70%-80%	75%-83%	70%-95%	Under R&D stage
	Next Generation Sequencing	4 hours	99.99%	NA	NA	96%	23 per sample
	ELISA	24 hours and/or above	95%	99.9%	97%	90%	10 per test
Futuristic	Artificial Intelligence	NA	90%	60%-95%	NA	90%	Under R&D stage
	Speech Recognition	NA	80%	86%	NA	79%	Under R&D stage
	3D- Facial Photography	NA	76%	86%-91%	NA	97%	Under R&D stage

ELISA: Enzyme linked immunosorbent assay; R&D: Research and development; NA: Not Available.

and a sensitivity of 86.8% in high intensity snorers [60]. There are microelectro mechanical system (MEMS)-based sensors using piezo-sensors that are capable of detecting the airflow of the patient. This sensor can detect change in air pressure of nasal airflow that is converted to a corresponding electrical signal by the transducer component of the sensor and processed for signal processing. The signal is then compared with a pre-set threshold value. This helps in identifying a single event of apnea [61]. The piezoelectric sensors are in general compact in size, cost-effective, and efficient. However, there are a few limitations to the use of piezo sensors such as the connections of the sensors with the body might cause discomfort and inconvenience to the patient during sleep. Moreover, the presence of disparity between the data obtained through piezo sensors and natural state of sleep should also be taken into consideration. Furthermore, piezo sensors are incapable of detecting other types of sleep apnea such as central and mixed for which more advanced sensors with improved algorithms need to be developed. Finally, since snoring is a major symptom of OSA, lack of snoring might be indicative of underestimation of AHI [62].

The growing applications of detection/management techniques such as smart pillows and a variety of sensors indicates the likelihood of accurate measurement of sleep variables such as AHI, snoring sounds, breathing patterns, etc. As opposed to the gold standard PSG that has its own limitations, modern techniques are non-invasive keeping in mind the comfort of the patient while being diagnosed. However, these modern devices are yet to precisely diagnose the disease and its related comorbidities. There's a lot of room to improve and develop portable multiplexed tools that can directly detect OSA and other comorbidities linked to this disease.

Table 1 below depicts the various modern and futuristic detection methods in contrast to the conventional method of detection of OSA.

3.5. Pitfalls

The above-mentioned modern detection methods have immense applications and advantages (specificity, less time consuming, cost-effectiveness, *etc.*) in the detection of OSA and associated biomarkers. However, they possess a few limitations as well.

(1) Home sleep apnea testing (HSAT) is unable to diagnose other sleep disorders, provides discomfort to the patient due to prolonged use, and improper evaluation using HSAT may result in inconclusive readings requiring repeat studies.
(2) Sleep tracking through smart wearables is challenging due to battery limitations as well as the limited number of sensors available to procure information about sleep disorders [63].
(3) Biomotion sensors have showcased their relevance in OSA detection, but there are a few limitations to their application such as periodic limb movements in OSA patients might lead to inconclusive results in sleep/wake patterns [64].
(4) Microarrays are rendered less useful due to requirement of large sample volumes and prolonged incubation times as well as limited detection sensitivity.

Therefore, it is imperative to design prompt and accurate methods of detection of sleep disorders that overcome can the above-mentioned challenges as well as encompass all the necessary parameters of sleep/wake patterns.

4. New age detection methods – a futuristic direction

Figure 1 represents a pictorial depiction of the conventional, modern and futuristic methods of OSA detection. New age detection methods are the current need of the hour for OSA detection. Screening strategies such as molecular markers are vital in the detection of diseases and identification of these biomarkers in body fluids is essential for prompt and early diagnosis as well as systematically monitored personalized therapeutics. Other methods such as use of artificial intelligence, 3D facial photography, and speech recognition have been discussed in the further sections.

4.1. Artificial intelligence

With the growing burden of OSA owing to under diagnosis among OSA patients, development of effective and accurate screening methods is becoming the need of the hour. The sleep medicine fraternity is consistently striving to achieve prompt diagnosis of OSA by developing state-of-the-art techniques such as biosensors, smart pillows, wearable devices,

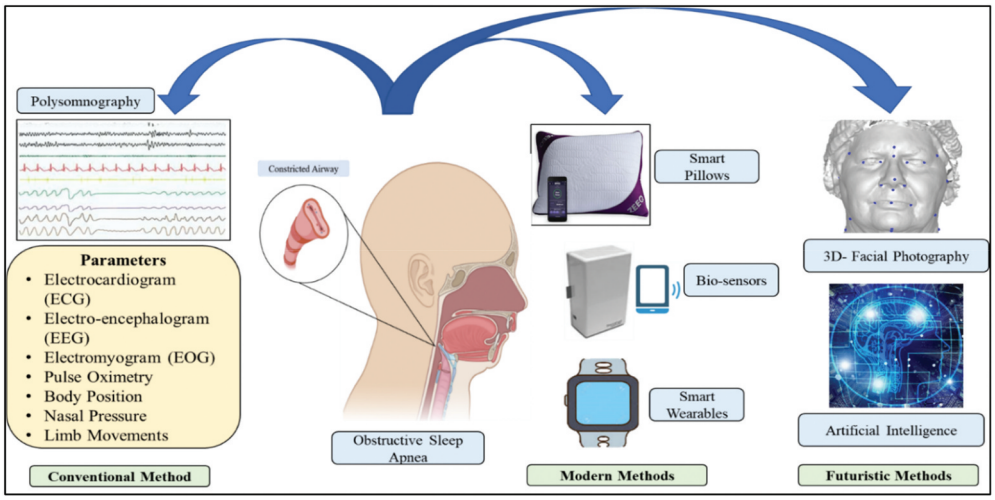

Figure 1. Conventional vs modern and futuristic detection of OSA. OSA is conventionally diagnosed using polysomnography, however, modern and futuristic methods of detection such as smart pillows, smart wearables, biomotion sensors as well as facial photography and artificial intelligence might be the next generation techniques adopted for prompt diagnosis of OSA.

etc. Recent reports have indicated that futuristic techniques such as speech recognition, three dimensional (3D) facial photography and artificial intelligence (AI)-based methods could be used proficiently to detect OSA [65–67]. Moreover, latest management strategies including hypoglossus nerve stimulation and expiratory positive airway pressure have been observed to be beneficial in treating OSA [68].

4.2. Biomarker-based detection and clinical relevance

Biomarkers can be detected for any chronic or life-threatening disease. However, detection of biomarkers with high precision is yet challenging due their presence in low concentrations mixed with different complex biomolecules. But it is to be noted that early diagnosis gives better success rates of cure. The ultimate goal for the use of biomarker-based detection technology lies in the development of reliable, cost-effective, and precise detection, more beneficially a portable bed side kit that does not need skilled manpower. Thus, by using biomarker detection technologies, doctors can select precise and accurate therapy for their patients. In addition, it can aid the doctors to effectively monitor the disease progression and its recurrence. Furthermore, it is also understood that there are very few diseases that can be validated by a single signature marker. Thus, the discovery of novel and validated biomarkers is immensely needed for early diagnosis. More importantly, development of technologies that can concurrently detect multiple biomarkers with high sensitivity and selectivity is highly inevitable. Multiplexed biomarker detection promises a new, personalized approach toward early detection and treatment follow-Up in several diseases. The most common type of biomarkers studied and identified are protein, DNA, RNA, and enzymes.

4.2.1. Protein biomarkers

Growing evidence has been shown the potential of biomarkers in detection of OSA. Till date the potential biomarkers for OSA studied include C-reactive protein (CRP), tumor necrosis factor (TNF)-α, IL-6, IL-8, and cell adhesion molecules (CAMs) among protein biomarkers. To ensure prompt and efficient detection of biomarkers for diseased conditions, various detection techniques have been developed such as enzyme linked immunosorbent assay (ELISA), surface plasmon resonance, mass spectrometry, microarrays, *etc* [69–72]. Methods like ELISA detect biomarkers in serum and biological fluids. However, there a few limitations to this detection method such as binding capacity and the specificity which depends on the immobilization chemistry. Moreover, reduced activity of proteins, requirement of toxic reagents of immobilization, and complex chemistry, makes the use of ELISA a big concern [73].

Moreover, microarrays have been widely used to identify gene expression patterns associated with molecular signatures of OSA. Superoxide dismutase (SOD) 1 and 2 have been identified to be dysregulated in OSA patients as corroborated by microarray analysis [74].

Sleep deprivation and OSA syndrome severely escalates the levels of these inflammatory biomarkers [75–80]. Elevated levels of these protein markers have also been validated in several other pathological conditions, that include viral, bacterial pathogenesis and diseases like arthritis, CVD, metabolic disorders, *etc*. A recent meta-analysis has shown the effects of CPAP therapy on patients with OSA and has shown a drop in the inflammatory profile in these patients [81]. The literature suggests that bariatric surgery (BS) is an efficient treatment method undertaken to bring down the inflammatory marker levels in patients with OSA [82]. CRP is a vital inflammation marker synthesized in the liver as a response to inflammatory occurrences and regulated by IL-6. An elevated level of CRP in blood is used as a benchmark for inflammation. Doctors usually prescribe a simple blood test for checking the CRP levels of the patient. Healthy patients usually have a CRP level of 1–3 mg/L and less than 1 indicates low cardiovascular risk, whereas more than 3 mg/L CRP levels indicate high risk of cardiovascular diseases. Poor sleeping

habits that are a resultant of OSA and hypertension, which is a major risk factor for CVD, results in an increase in hs-CRP levels [76,83–88].

Similarly, TNF-α is known to trigger inflammatory responses that further cause many problems such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, etc. It is one of the most important cytokines involved in sleep regulation [75,89,90]. Like CRP, TNF-α levels are also heightened in sleep apnea subjects [89,91]. Gene polymorphisms in TNF-α have also been seen to be significantly higher in obese patients with OSA [92].

Interestingly, IL-8 is a vital chemokine secreted mainly by macrophages as well as certain other cells such as epithelial and endothelial cells. IL-8 levels are elevated in patients with OSA, regardless of obesity [93] and are known to fall after the CPAP therapy, and thus, lowering the risk of cardiovascular diseases [94–96]. Snoring causes vibration of the upper airway resulting in inflammation causing an increase in levels of IL-8 [97].

Decreased levels of biomarkers also indicate the status of OSA as corroborated by different studies. Klotho is an anti-inflammatory, anti-aging and anti-oxidative protein secreted mainly by the kidneys. Reduced levels of klotho protein have been observed in patients with OSA and associated with overnight hypoxemia and presence of hypertension, suggesing that chronic intermittent hypoxia lowers klotho levels in OSA and contributes to hypertension development [98]. Similarly, decreased levels of survivin [99], vitamin D [100], and markers of the plasminogen system [101] were reported in OSA patients, indicating their association with disease severity.

Cytokine levels in the breath condensates of OSA patients have also been proven to be potential biomarker candidates for detecting the severity of OSA. Li *et al.* reported the biomarker levels of IL-6, IL-10, TNF-α, and 8-isoprostane in exhaled breath condensates (EBC) and serum, and deduced that IL-6 and IL-10 levels in EBC were directly correlated with the severity of OSA [102]. In addition, electronic nose technology is being used to diagnose OSA in patients using their breath samples [31]. Studies revealed the proficiency of electronic noses in the detection of volatile organic compounds (VOC) of OSA patients with an accuracy of 77% and a sensitivity of 93% [103,104].

Figure 2 depicts the various kinds of biomarkers studied in OSA.

4.2.2. RNA biomarkers

Another class of widely studied biomarkers are miRNAs which are key players of altered gene expression. Very few studies pertaining to OSA linked RNA markers, such as miRNA has been performed. Our recently published work on the involvement of miRNAs in obesity associated OSA have elaborated on the role of miR-21, miR-27, miR-29, and let-7 as potential biomarkers in OSA [105]. Our previously published review article demonstrates the role of miRNAs along with other DNA, RNA and protein biomarkers in OSA [106]. Moreover, miRNAs in OSA have been a crucial topic of research all around the globe. Only a handful of studies have provided insights about the involvement of miRNAs in OSA and related conditions. For instance, miR-664a-3p has been acknowledged as a biomarker of atherosclerosis in OSA subjects [107]. Moreover, miR-130a contributed in the progression of OSAHS-associated pulmonary hypertension (PHT) by suppressing the activity of growth arrest-specific homeobox gene (GAX) [108]. miRNA profiling suggested a decrease in circulating concentrations of miR-181a, miR-199b, miR-345, miR-133a, miR-340, and miR-486-3p in OSA [109]. miR-1254 in heart

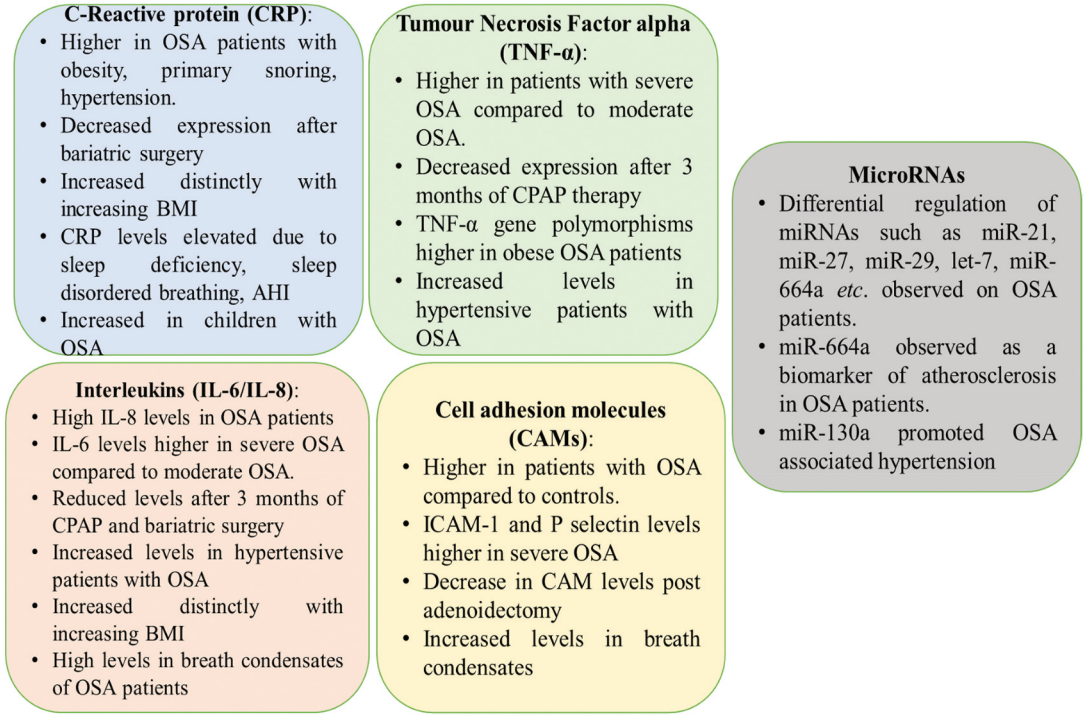

Figure 2. Biomarkers of OSA. OSA associated biomarkers such as CRP, TNF-α, interleukins and CAM's have been found to be elevated in OSA.

failure and miR-320e in myocardial ischemia were also independently associated with severe OSA as prognostic markers [110]. Moreover, our previous studies revealed a significant differential expression in miRNA levels in OSA patients and healthy non-OSA cohort. We observed a marginal increase in the expression of miR-21, whereas a significant decrease in the expression levels of miR-27, miR-29, and let-7 in peripheral blood mononuclear cells derived from OSA patients [105,111].

OSA being associated with clinical conditions such as cardiovascular disorders, hypertension, and cardiac diseases along with metabolic disorders such as diabetes. As such it is imperative to do miRNA profiling in detecting these co-existing morbidities. Also, a variety of other sleep variables and apnea events need to be assessed in depth. For therapy commitment, usage time is a major factor to consider. These modern techniques and smartphone-based diagnostics also need to be in compliance with the sleep specialist. Therefore, more information and education on this aspect of detection is required keeping in mind the best interests of the broader public.

4.3. Other new age detection methods

Among the recently developed detection systems are biosensors that have proven to be efficient in biomarker detection. It is evident from various researches that a well-designed nano-biosensor can identify small traces of specific biomarkers to develop detection tools that are reliable, cost effective, and capable of prompt detection. Another advantage of these detection tools is that it allows the physicians to choose the precise therapy needed for the patient further allowing them to efficiently monitor the disease progression. The biosensors can be portable and highly reliable OSA diagnostic tools in future, where a panel of markers can be detected in a single chip with high sensitivity and accuracy.

With the advent of modern detection methods such as nanoparticle-based detection, quantum dot technology, 9 G DNA technology [73], the detection of biomarkers has become much ensuring for prompt disease diagnosis. Nanoparticles (NPs), due to their small size, enter the body through inhalation, ingestion or via injections and interact with biomolecules. Evidence suggests that NPs have been used for detection of obesity and type 2 diabetes associated genes such as NAMPT and INSIG2, indicating their significance in the future of disease detection [112]. Similarly, quantum dots (QDs) which are a class of inorganic, fluorescent nanoparticles have been used in biomedical research. With advantages such as nano-scale size, broad excitation spectra, narrow emission spectra, and longer fluorescence half-life, QDs can be employed as exceptional probes. The literature suggests that QD-based detection of *prohibitin* in obese rats, demonstrated their potential as nanocarriers in anti-obesity drugs [113]. Moreover, 9 G DNA technology uses the principle of oligonucleotide hybridization and detection based on the presence of 9 consecutive guanine bases (9 G). However, this technology is still under extensive research to ensure its viability as a promising method of detection.

4.4. Existing challenges

Considering the multitude advantages of these futuristic detection methods, however, a few pitfalls of these techniques have also come to light.

(1) 3D imaging technologies are based on correlations with the AHI, however, as corroborated by a study in 2005, PSG indices are not concordant with the crucial OSA specific clinical characteristics such as sleepiness and the overall quality of life [114].
(2) A recent study by Kainulainen *et al.* demonstrated that oxygen desaturation severity, might better correlate with the excessive sleepiness than AHI, and being capable of predicting OSA related consequences [115]. Therefore, further investigations should aim at integrating oximetry and facial photography to achieve paramount accuracy in OSA detection.
(3) Toxicity issues, large size, short life-span, and nonspecific detection of QDs limit their biomedical imaging and therapeutic applications [116].
(4) Limitations of artificial intelligence in sleep medicine include complexity of AI data pertaining to sleep patterns and sleep disorders [117].

5. Management of OSA

The primary goal of managing OSA is alleviating the signs and symptoms, improving sleep quality, and normalizing the apnea-hypopnea index (AHI) and saturated oxygen level in patients. The most preferred approach recommended by Clinicians is the use of CPAP device. Often lifestyle management and surgical procedures are also recommended. Currently, smart pillows are also available on the market for monitoring sleep disorders.

5.1. Continuous positive airway pressure

Continuous positive airway pressure (CPAP) has shown tremendous growth in the last few years. The main purpose of positive airway pressure devices is to support and maintain the upper airway intact and unobstructed by slowly increasing the upper airway pressure above a threshold value, which is usually the pressure below which the airway has a tendency to collapse [118]. In accordance with the guidelines issued by the American Academy of Sleep Medicine (AASM) and National Institute of Health and Care Excellence (NICE), CPAP is the most commercially adopted mode of treatment for OSA patients [119,120]. AASM recommends using the PAP therapy, in comparison to no therapy to treat OSA in adults with excessive daytime sleepiness. Moreover, NICE recommends the use of CPAP for mild OSA only if the related symptoms are affecting the quality of life and any other lifestyle advice or treatment option has been observed to be unsuccessful in treating OSA. CPAP (Figure 3) is ordinarily recommended as a nasal mode of treatment for patients with moderate-to-severe OSA. CPAP has been shown to reduce the number of respiratory events and eventually AHI. Additionally, CPAP

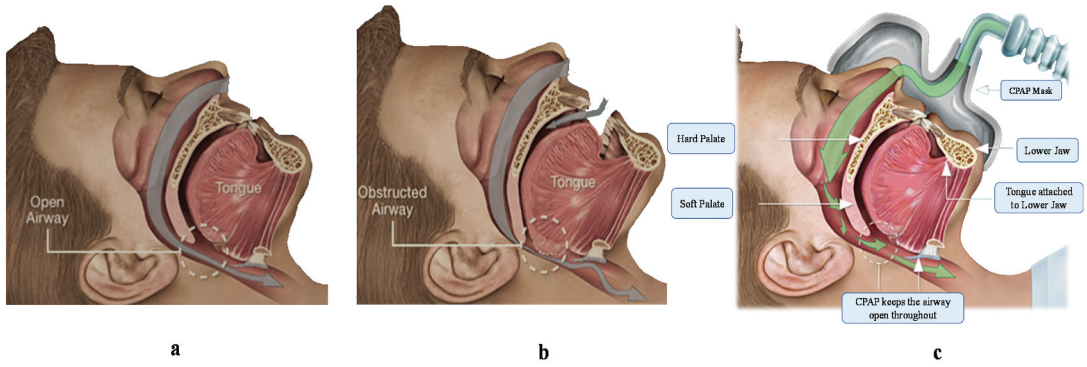

Figure 3. Pictorial representation of a (a) normal airway, (b) obstructed airway (OSA), and (c) OSA management using continuous positive airway pressure (CPAP) therapy.

improves the daytime symptoms, apart from other parameters such as saturated oxygen [121]. Interestingly, CPAP has also been effective in reducing OSA-associated comorbidities such as cardiovascular diseases and diabetes [122,123]. CPAP treatment has also been seen to normalize the circulating nitric oxide levels in hypertension [124]. Moreover, in OSA-associated metabolic syndrome, CPAP has also been proven to be effective in reversing insulin resistance and improving insulin sensitivity [125]. Literature cites that CPAP therapy also reduces the circulating microvesicles levels thereby reducing the risk of metabolic and cardiac complications [126]. It has also been observed that CPAP therapy improves metabolic function in T2DM patients, thereby decreasing insulin resistance [127]. CPAP is also beneficial in a plethora of ways as it is capable of promoting daytime alertness and concentration. However, there are a few limitations associated with the use CPAP such as it is expensive, continuous use (every night), mask discomfort, nasal congestion, and nose and throat soreness.

5.2. Lifestyle moderation

Obesity has been regarded as one of the most common and potential risk factors for OSA [128]. Food habits such as increased calorie intake especially high in carbohydrates have been seen to be associated with OSA severity [129]. Several studies have demonstrated that weight loss achieved through very low calorie diet intake has been successful in alleviating the symptoms of OSA by improving the BMI and AHI [130]. Very low calorie diet accompanied with active lifestyle not only results in weight loss and OSA tolerance but also improves other existing comorbidities such as hypertension, cardiovascular diseases, and diabetes by improving a range of cardiovascular variables [131]. Mediterranean diets have been observed to be beneficial for weight loss as they promote satiation and encourage adherence to calorie-restricted diets [132]. Moreover, surgically induced weight loss has also been associated with improvements in OSA severity, associated clinical conditions, and overall quality of life [133]. However, in morbidly obese OSA patients, only weight loss cannot completely cure OSA and additional therapies are required. In addition to diet mediated weight loss, changing of sleeping postures has been advised to alleviate the symptoms of OSA. Supine position increases the likelihood of the tongue falling back into the airway as a result of gravity, thereby blocking the airway. Therefore, positional therapy is advised in OSA patients to reduce the apneic events from occurring.

5.3. Surgical procedures

Another crucial tool for management of OSA is surgical intervention, which improves airway obstruction, sleep quality, AHI, and saturated oxygen levels. Different types of surgeries are employed depending on the sites of obstruction. Nasal surgeries are conducted for patients with nasal obstructions and include surgeries of the septum, nasal valve, and sinus [134]. The sole purpose of these surgeries is to better the nasal airflow thereby improving sleep quality. Oropharyngeal surgeries also known as *uvulopalatopharyngoplasty* (UPPP), target the enlarged tonsils of the patient and are the most performed surgeries. In general, tongue surgeries have been shown to reduced daytime sleepiness symptoms [134]. The third most important surgery type is maxillomandibular advancement (MMA), also known as craniofacial surgery. MMA involves the adjustment of the orientation of jaws and interestingly, it is by far the most successful surgery with a cure rate of more than 40%. UPPP has been observed to be beneficial in lessening the cardiac burden by improving carotid atherosclerosis and arrhythmia-related parameters in OSA patients [135,136]. Reports suggested that UPPP also lowered the risk of cardiac complications such as congestive heart failure and atrial fibrillation in OSA patients, eventually improving cardiac health [137]. However, surgical methods have a few limitations. Many anesthetic medications relax the throat muscles which eventually worsening OSA during the procedure. Other surgery-associated risks include infection, excessive bleeding, additional respiratory problems, allergic reactions, and speech difficulties [138].

5.4. Oral appliances

Therapy *via* oral appliances (OA) is being increasingly prescribed by the doctors as a noninvasive mode of treatment for patients with mild-to-moderate OSA. Further, patients who are unable to respond to CPAP are also advised oral appliance-

based therapy [139]. These appliances improve the upper airway configuration as well as prevent the airway from collapsing by alteration of the tongue and jaw position. Commonly, oral appliances work by either holding the lower jaw in the anterior position or adjustment of the tongue and are hence termed as mandibular advancement devices (MAD) and tongue retaining devices (TRDs), respectively [140]. Patients with MAD therapy exhibit mild side effects initially such as dry mouth, discomfort, muscle tenderness, irritation, *etc*., however, these symptoms are mostly temporary and resolve within a few days. More importantly, MADs are effective at reducing snoring, improving the AHI and lowering the severity of OSA by adjusting the position of the lower jaw and the tongue, provided the device is used appropriately and continuously. Studies demonstrate the effectiveness of MADs by revealing a 50% decrease in AHI in nearly one-thirds of the patients undergoing MAD therapy [141]. Oral appliance therapy has been reported to have beneficial effects on cardiac function thereby reducing the cardiovascular associated mortality [142]. Literature also cites that endothelial dysfunction is a key predictor of cardiovascular complications. In relation to this, Lin *et al*. demonstrated that use of MAD therapy improved endothelial dysfunction in OSA patients [143]. Further, the health outcomes with CPAP and MAD are comparable, reflecting a greater nightly adherence to MAD as compared to CPAP. However, CPAP has been reported to reduce OSA severity to a greater extent than MAD therapy in patients with mild to severe OSA. Treatment with MADs is a viable and effective alternative for OSA, but strict monitoring is warranted due to variation in the patient response to therapy.

Table 2. Salient features and limitations of OSA management.

Method	Benefits	Limitations
Continuous Positive Airway Pressure (CPAP)	Better heart health, lower risk of diabetes, prevention of heart diseases, prevention of road accidents, improved daytime alertness, improved focus, removed snoring, prevention of stroke, improved weight loss, improved OSA severity, stronger immunity, improved work performance, better sleep, reduced risks of CVD	Cost ineffectiveness, continuous use (every night), mask discomfort, nasal congestion and nose and throat soreness
Lifestyle Moderation	Improvement in OSA, lower risk of CVD and diabetes, better health.	Morbidly obese OSA patients- only weight loss cannot completely cure OSA and additional therapies are required
Surgical Procedures	Improved OSA severity, reduced risk for early mortality, reduced CVD risk, improved life quality	Relax the throat muscles, eventually worsening OSA; risk of infection, excessive bleeding, additional respiratory problems, allergic reactions and speech difficulties
Smart Pillows	Improved total AHI, reduced snoring, low cost	Pillows are dependent on body posture, weight and other comorbid conditions; extensive research required for determining the effectiveness

5.5. Positional therapy

Positional therapy is based on the changing of sleeping positions of the patients to alleviate the symptoms and reduce the OSA severity. The frequency of apneic events increases during sleeping in a supine position; therefore, a side position is generally advised. During supine position, the tendency of the airway to collapse increases due to the effect of gravity. Over the years, a plethora of positional therapies have been suggested to OSA patients to relieve the symptoms and reduce the severity such as alarm systems, behavioral therapy, tennis ball technique, backpack technique, vibrating devices on the neck or chest, *etc* [144]. However, studies report greater AHI improvements with CPAP than positional therapy [145].

5.6. Smart pillows and beds

Adjustable smart pillows have entered the market for both management and treatment purposes [146]. This diagnostic method is noninvasive, cost-effective, and portable. The smart pillow consists of an oxygen sensor that detects the respiratory events in real time. The use of smart pillows can be beneficial for the patients in two ways. First, the pillow adjusts its height automatically by supporting the patients' neck allowing a change in the angle of the airway to avoid obstruction, thereby alleviating apneic episodes. Second, the resizing of the pillow triggers the sleep center in the brain to emit signals followed by activation of the genioglossus muscle of the throat which eventually prevents further episodes of apnea [146]. A few smart pillows come equipped with noise cancellation technologies and inbuilt Bluetooth speakers for listening to music thereby relaxing the body. Smart pillows have emerged as a promising strategy for a healthier sleep pattern. However, a deeper investigative approach needs to be followed to assess and improve its effectiveness toward management of OSA on larger patient cohorts. A plethora of smart pillow companies such *as iSense Sleep Smart Pillow, Sunrise Smart Pillow, 10minds, Smart Nora, Goodnite Smart Anti-Snore Pillow, DreamPad, ZeeQ Smart Pillow,* and others have made smart pillows available in the market for diagnosis and management of OSA. Smart pillows are widely used in smart home systems due to their cost effectiveness as they can be purchased for as low as 40 USD with prices as high as 299 USD.

Even smart beds such as *Sleep Number 360* priced at a range of 999 USD has gained immense popularity. It functions by adjusting the firmness by automatically sensing the patient's posture to provide greater comfort. In response to the patient's snoring, it has the capability to adjust the head side of the bed upwards. Such smart beds are equipped with built-in sensors that monitor the patient's heart rate, breathing, movement and quality of sleep.

Although these smart beds and pillows have been observed to be beneficial for OSA management, however, CPAP is still the most effective treatment strategy for OSA.

5.7. Comparative analysis

Considering the above methods of management of OSA and the respective salient features and limitations they pose, a comparison has been drawn as summarized in Table 2.

6. Conclusion

OSA is a global concern of paramount importance to the sleep medicine fraternity due to inconsistency in its prevalence attributed to lack of awareness among patients as well as clinical ramifications associated with it such as hypertension, cardiovascular and cerebrovascular diseases, diabetes, *etc*. Due to the aggravation of these comorbidities, addressing the prevalence of OSA in the global population is becoming the need of the hour.

Different approaches have come up in the recent years with the primary aim of prompt OSA detection, considering the limitations of the already available polysomnography analysis. PSG-based diagnosis on the basis of AHI and frequency of arousals have not been observed to be reliable in terms of predicting the degree of physical impairment with sleep disordered breathing. New diagnostic modalities capable of overcoming the challenges with PSG are highlighted.

The modern detection methods have mainly emphasized on portability, cost-effectiveness, and ease in usability. Such devices include wearable devices, biomotion sensors, radiowave-based sensors, *etc*. Some of these portable technologies, can prove to be handy tools for patients to self-diagnose themselves. However, sensitivity of these techniques is yet to be understood and evaluated closely and may need further improvement. These methods are mostly focusing on portability, cost effectiveness, and patient's comfort. However, considering the growing evidence on OSA, detection methods should also be aimed at encompassing patient-related parameters such as sensitivity, accuracy, and most importantly, the ability to identify the possible consequences of OSA. From an overall analysis of our review, it is understood that future directions must be explored to develop new and efficient strategies aimed at OSA screening in the population and management by overcoming these limitations.

Futuristic and new-age methods of detection such as nanotechnology-based detection, biomarker detection platforms, quantum dot technology, 9 G DNA technology, speech recognitions, three-dimensional facial photography, and artificial intelligence-based methods have the potential to be highly proficient in detecting OSA. To bring such futuristic tools to the broader public, more in-depth investigations need to be performed to understand the pathophysiology of OSA that will assist in providing critical information for its diagnosis and management. Furthermore, concurrent detection of a panel of molecular markers such as those derived from exosomes could do wonders in diagnosing OSA and several related comorbidities.

7. Expert opinion

Although OSA is an exceedingly common sleep disorder, it remains unrecognized and undiagnosed in most of the population attributed to lack of its awareness and hesitation in patients to disclose the disease. It not only puts forward a negative impact on the patient's quality of life but also adversely affects partner's life. It is crucial to know that OSA is associated with several chronic and life-threatening comorbidities, such as, diabetes, cardiovascular disease, depression, *etc*. Due to these consequential clinical morbidities and outcomes, OSA and its management is continuously posing as a global economic burden on healthcare systems. The socio-economic impact of sleep disorders such as OSA is a significant burden globally. Increased health care utilization is seen in patients with sleep disordered breathing. As 90% of the OSA patients go undiagnosed and untreated, the burden of OSA increases drastically. Due to the increased morbidity status of OSA, the medical costs increase substantially. Thus, proper management of OSA is of utmost importance that will provide widespread benefits not only to the patients, but also to the society.

As of current scenario, polysomnography is known to be the gold standard method to diagnose OSA in any patient. Although sensitive, but poses limitations such as patient discomfort and need for hospitalization and skilled operators. However, access to this procedure is restricted due to requirement of special sleep institutions equipped with skilled specialists. As a result, suspected OSA patients have to wait for months before being diagnosed and able to initiate medical therapy or CPAP. However, it is noteworthy that future technology will be better in a multitude of ways and simpler and a significant number of OSA patients will be catered to in primary care.

Thus, there is an imperative need of new diagnostics for screening of asymptomatic OSA patients as well to reduce the risk of several associated comorbidities. In this direction, home testing tools, wearable sensors and trackers, *etc*., are available in market but sensitivity of detection as compared to polysomnography is questionable. Several studies off-late indicate that molecular marker-based diagnosis of OSA can be a remarkable solution that holds the flavors of high sensitivity as the conventional polysomnography and portability as the modern tools. However, detection of such markers on a single platform is still under research and needs validation. With the advent of *smart* medical diagnostic methods, prompt detection of sleep apnea can be easily achievable. Considering the pandemic diseases when the hospital-based sleep centers being forced to shut down, such home-based detection systems and new digital technologies would become the need of the hour. However, validation in a larger patient cohort needs to be performed before they are used clinically.

Since OSA is not permanently curable, there have been several management strategies to control the disease and its severity linked to the chronic comorbidities. Products like smart pillows/mattresses, smart wearables such as wristbands, rings, headbands, and eye-patches are available as an alternative and have shown promising results, but the extent of their success is yet to be analyzed by better understanding their working principle and comparison with the existing technology.

Overall, a collective and pooled piece of information pertaining to in-depth comparison between Polysomnography and newer detection methods such as wearables, biomotion sensors, artificial intelligence, *etc.,* and the very promising molecular marker-based diagnostics is warranted to bridge the existing gaps in knowledge.

Acknowledgments

The authors - S.K., R.N. and S.B. would like to extend their gratitude To Amity University Uttar Pradesh for research support. The author S.K. would also like to acknowledge Indian Council of Medical Research for the Senior Research Fellowship (No. 3/1/2/6(COPD)/2018-NCD-1).

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

1. Kalra M, Inge T, Garcia V, et al. Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. Obes Res. 2005;13(7):1175–1179.Epub 2005/ 08/04. PubMed PMID: 16076986.
2. Agrawal S, Gupta R, Lahan V, et al.Prevalence of obstructive sleep apnea in surgical patients presenting to a tertiary care teaching hospital in India: a preliminary study.Saudi J Anaesth.2013;7 (2):155–159;Epub 2013/ 08/21. PubMed PMID: 23956715; PubMed Central PMCID: PMC3737691;
3. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019;7(8):687–698.
4. Phillips CL, O'Driscoll DM. Hypertension and obstructive sleep apnea. Nat Sci Sleep. 2013;5:43.
5. Andrade AG, Bubu OM, Varga AW, et al. The relationship between obstructive sleep apnea and Alzheimer's disease. J Alzheimers Dis. 2018;64(s1):S255–S70.
6. Jehan S, Auguste E, and Pandi-Perumal SR, et al. Depression, obstructive sleep apnea and psychosocial health. Medicine and Disorders: International Journal. 2017; 1(3):00012.
7. Tietjens JR, Claman D, Kezirian EJ, et al. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. Journal of the American Heart Association. 2019;8(1):e010440.
8. Ahmad M, Makati D, and Akbar S. Review of and updates on hypertension in obstructive sleep apnea. Int J Hypertens. 2017;2017.
9. Sleep Apnea Statistics and Facts 2016.
10. Gozal D. Serum, urine, and breath-related biomarkers in the diagnosis of obstructive sleep apnea in children: is it for real? Curr Opin Pulm Med. 2012;18(6):561–567.
11. Halbower AC, Degaonkar M, Barker PB, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med. 2006;3(8):e301.
12. Gottlieb DJ, Chase C, Vezina RM, et al. Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. J Pediatr. 2004;145(4):458–464.
13. Chan J, Edman JC, Koltai PJ. Obstructive sleep apnea in children. Am Fam Physician. 2004;69(5):1147–1154.
14. Marcus CL, Brooks LJ, Ward SD, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2012;130(3):e714–e55.
15. Norman D, Loredo JS. Obstructive sleep apnea in older adults. Clin Geriatr Med. 2008;24(1):151–165.
16. Martínez-García MÁ, Chiner E, Hernández L, et al. Obstructive sleep apnoea in the elderly: role of continuous positive airway pressure treatment. Eur Respir J. 2015;46(1):142–151.
17. Glasser M, Bailey N, McMillan A, et al. Sleep apnoea in older people. Breathe. 2011;7(3):248–256.
18. Semelka M, Wilson J, Floyd R. Diagnosis and treatment of obstructive sleep apnea in adults. Am Fam Physician. 2016;94(5):355–360.
19. Peppard PE, Young T, Palta M, et al.Prospective study of the association between sleep-disordered breathing and hypertension.N Engl J Med.2000;342(19):1378–1384. Epub 2000/ 05/11. PubMed PMID: 10805822.
20. Turmel J, Series F, Boulet LP, et al. Relationship between atherosclerosis and the sleep apnea syndrome: an intravascular ultrasound study. Int J Cardiol. 2009;132(2):203–209. Epub 2008/ 01/ 29. PubMed PMID: 18221805.
21. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation. 2004;110(4):364–367. Epub 2004/ 07/14. CIR.0000136587.68725.8E [pii]. PubMed PMID: 15249509.
22. Todd K, McIntyre WF, Baranchuk A. Obstructive sleep apnea and atrial fibrillation. Nat Sci Sleep. 2010;2:39–45. Epub 2010/ 01/01. PubMed PMID: 23616697; PubMed Central PMCID: PMC3630930.
23. Kent BD, Grote L, Ryan S, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. Chest. 2014;146(4):982–990. Epub 2014/ 05/ 17. PubMed PMID: 24831859.
24. Punjabi NM, Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. Am J Respir Crit Care Med. Epub 2008/ 11/18. DOI:10.1164/rccm.200809-1392OC. PubMed PMID: 19011148; PubMed Central PMCID: PMC2633056 2009;179(3):235–240.
25. Louis M, Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. J Appl Physiol. (1985). 2009;106(5):1538–1544. Epub 2009/ 03/07. 10.1152/japplphysiol.91523.2008 91523.2008. PubMed PMID: 19265062; PubMed Central PMCID: PMC2681331.
26. Punjabi NM, Aurora RN, Patil SP. Home sleep testing for obstructive sleep apnea: one night is enough! Chest. Chest. 2013;143(2):291–294.
27. Jayaraj R, Mohan J, Kanagasabai A. A review on detection and treatment methods of sleep apnea. J Clin Diagn Res. 2017;11(3): VE01.
28. Penzel T, Schöbel C, Fietze I. New technology to assess sleep apnea: wearables, smartphones, and accessories. F1000Res. 2018;7:413.
29. Sharma M, Raval M, Acharya UR. A new approach to identify obstructive sleep apnea using an optimal orthogonal wavelet filter bank with ECG signals. IMU. 2019;16:100170.
30. Greulich T, Hattesohl A, Grabisch A, et al. Detection of obstructive sleep apnoea by an electronic nose. Eur Respir J. 2013;42(1):145–155.
31. Scarlata S, Pennazza G, Santonico M, et al. Screening of obstructive sleep apnea syndrome by electronic-nose analysis of volatile organic compounds. Sci Rep. 2017;7(1):1–8.
32. Finamore P, Scarlata S, Cardaci V, et al. Exhaled breath analysis in obstructive sleep apnea syndrome: a review of the literature. Medicina (B Aires). 2019;55(9):538.

33. Bikov A, Hull JH, Kunos L. Exhaled breath analysis, a simple tool to study the pathophysiology of obstructive sleep apnoea. Sleep Med Rev. 2016;27:1–8.
34. Sannino G, De Falco I, De Pietro G. Monitoring obstructive sleep apnea by means of a real-time mobile system based on the automatic extraction of sets of rules through differential evolution. J Biomed Inform. 2014;49:84–100.
35. Singh J, Mims N. Screening tools for the obstructive sleep apnea for the cardiovascular clinician. Am Coll Cardiol. 2015.
36. Amra B, Rahmati B, Soltaninejad F, et al. Screening questionnaires for obstructive sleep apnea: an updated systematic review. Oman Med J. 2018;33(3):184.
37. Rundo JV.Obstructive sleep apnea basics.Cleve Clin J Med.2019;86 (9Suppl 1):2–9;Epub 2019/ 09/12. PubMed PMID: 31509498.
38. Jafari B, Mohsenin V.Polysomnography.Clin Chest Med.2010;31 (2):287–297;Epub 2010/ 05/22. PubMed PMID: 20488287;
39. Rundo JV, Downey R 3rd. Polysomnography. Handb Clin Neurol. 2019;160:381–392. Epub 2019/ 07/07. PubMed PMID: 31277862.
40. Randerath W, Bassetti CL, Bonsignore MR, et al. Challenges and perspectives in obstructive sleep apnoea: report by an ad hoc working group of the sleep disordered breathing group of the European respiratory society and the European sleep research society. Eur Respir J. 2018;52(3):1702616.
41. Kheirandish-Gozal L, Gozal D. The multiple challenges of obstructive sleep apnea in children: diagnosis. Current Opinion in Pediatrics. 2008;20(6):650–653.
42. Ben-Israel N, Tarasiuk A, Zigel Y. Obstructive apnea hypopnea index estimation by analysis of nocturnal snoring signals in adults. Sleep. 2012;35(9):1299–1305.
43. Dafna E, Tarasiuk A, Zigel Y. Automatic detection of whole night snoring events using non-contact microphone. PloS One. 2013;8 (12):e84139.
44. Kang S, Kim D-K, and Lee Y, et al. Non-contact diagnosis of obstructive sleep apnea using impulse-radio ultra-wideband radar. Scientific Reports. 2020;10(1):1–7.
45. Oliver N, and Flores-Mangas FJJ. Healthgear: automatic sleep apnea detection and monitoring with a mobile phone. Journal of Communications. 2007;2(2):1–9.
46. Papini GB, Fonseca P, van Gilst MM, et al. Wearable monitoring of sleep-disordered breathing: estimation of the apnea–hypopnea index using wrist-worn reflective photoplethysmography. Sci Rep. 2020;10(1):1–15.
47. Manoni A, Loreti F, Radicioni V, et al. A new wearable system for home sleep apnea testing, screening, and classification. Sensors (Basel). 2020;20(24):7014.
48. Yüzer A, Sümbül H, Polat K. A novel wearable real-time sleep apnea detection system based on the acceleration sensor. IRBM. 2020;41 (1):39–47.
49. Surrel G, Rincón F, and Murali S, et al., editors. Low-power wearable system for real-time screening of obstructive sleep apnea. 2016 IEEE Computer Society Annual Symposium on VLSI (ISVLSI). Pittsburgh, PA, USA. 2016: Ieee.
50. Van Steenkiste T, Groenendaal W, Dreesen P, et al. Portable detection of apnea and hypopnea events using bio-impedance of the chest and deep learning. IEEE Journal of Biomedical and Health Informatics. 2020;24(9):2589–2598.
51. Perez-Pozuelo I, Zhai B, Palotti J, et al. The future of sleep health: a data-driven revolution in sleep science and medicine. Npj Digit Med. 2020;3(1):1–15.
52. De Chazal P, Fox N, O'hare E, et al. Sleep/wake measurement using a non-contact biomotion sensor. J Sleep Res. 2011;20(2):356–366.
53. Zaffaroni A, De Chazal P, and Heneghan C, et al., editors. Sleepminder: an innovative contact-free device for the estimation of the apnoea-hypopnoea index. 2009 annual international conference of the IEEE engineering in medicine and biology society. Minneapolis, MN, USA. 2009: IEEE.
54. Crinion SJ, Tiron R, Lyon G, et al. Ambulatory detection of sleep apnea using a non-contact biomotion sensor. J Sleep Res. 2020;29 (1):e12889.
55. Yang X, Fan D, Ren A, et al. Sleep apnea syndrome sensing at C-band. IEEE J Transl Eng Health Med. 2018;6:1–8.
56. Kang S, Kim D-K, Lee Y, et al. non-contact diagnosis of obstructive sleep apnea using impulse-radio ultra-wideband radar. Sci Rep. 2020;10(1):1–7.
57. Lee H-K, Lee J, Kim H, et al. Snoring detection using a piezo snoring sensor based on hidden Markov models. Physiol Meas. 2013;34(5): N41.
58. Erdenebayar U, Park J-U, Jeong P, et al. Obstructive sleep apnea screening using a piezo-electric sensor. J Korean Med Sci. 2017;32 (6):893–899.
59. Davidovich MLY, Karasik R, and Tal A, et al., editors. Sleep apnea screening with a contact-free under-the-mattress sensor. 2016 computing in cardiology conference (CinC). Vancouver, BC, Canada. 2016: IEEE.
60. Perez-Macias JM, Tenhunen M, Värri A, et al. Detection of snores using source separation on an Emfit signal. IEEE J Biomed Health Inform. 2017;22(4):1157–1167.
61. Kumar P, Nithya V, Vimala J. Micro system with MEMS sensor for detecting sleep apnea. J Eng Appl Sci. 2016;11(3):2097–2101.
62. Erdenebayar U, Park JU, Jeong P, et al.Obstructive sleep apnea screening using a piezo-electric sensor.J Korean Med Sci.2017;32 (6):893–899;Epub 2017/ 05/10. PubMed PMID: 28480645; PubMed Central PMCID: PMCPMC5426252;
63. Camcı B, Ersoy C, Kaynak H. Abnormal respiratory event detection in sleep: a prescreening system with smart wearables. J Biomed Inform. 2019;95:103218.
64. Pallin M, O'hare E, Zaffaroni A, et al. Comparison of a novel non-contact biomotion sensor with wrist actigraphy in estimating sleep quality in patients with obstructive sleep apnoea. J Sleep Res. 2014;23(4):475–484.
65. Jacobowitz O, MacKay S. The faces of sleep apnea in the age of machine learning. J Clin Sleep Med. 2020;16(4):469–470.
66. Goldstein CA, Berry RB, Kent DT, et al. Artificial intelligence in sleep medicine: an American academy of sleep medicine position statement. J Clin Sleep Med. 2020;16(4):605–607.
67. Espinoza-Cuadros F, Fernández-Pozo R, Toledano DT, et al. Speech signal and facial image processing for obstructive sleep apnea assessment. CMMM. 2015;2015. DOI:10.1155/2015/489761
68. Foundation NS. The Latest Treatments for Obstructive Sleep Apnea. SleepFoundationorg. 2020. https://www.sleepfoundation.org/sleep-apnea/treatment/hypoglossal-nerve-stimulation.
69. de La Rica R, Stevens MM.Plasmonic ELISA for the ultrasensitive detection of disease biomarkers with the naked eye.Nat Nanotechnol.2012;7(12):821–824;Epub 2012/ 10/30. PubMed PMID: 23103935;
70. Law WC, Yong KT, Baev A, et al.Sensitivity improved surface plasmon resonance biosensor for cancer biomarker detection based on plasmonic enhancement.ACS Nano.2011;5(6):4858–4864;Epub 2011/ 04/23. PubMed PMID: 21510685;
71. Lee HJ, Wark AW, Corn RM.Microarray methods for protein biomarker detection.Analyst.2008;133(8):975–983;Epub 2008/ 07/23. PubMed PMID: 18645635; PubMed Central PMCID: PMCPMC2738748;
72. Von Neuhoff N, Pich AJDDTT. Mass spectrometry-based methods for biomarker detection and analysis. Drug Discovery Today. Technologies. 2005;2(4):361–367.
73. Nimse SB, Sonawane MD, Song K-S, et al. Biomarker detection technologies and future directions. The Analyst. 2016;141(3):740–755.
74. Arnardottir ES, Mackiewicz M, Gislason T, et al. Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep. 2009;32(4):447–470.
75. Archontogeorgis K, Nena E, Papanas N, et al. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. Pulm Med. 2014;2014:930535. Epub 2014/ 12/30. PubMed PMID: 25538852; PubMed Central PMCID: PMC4265695.
76. Matthews KA, Zheng H, Kravitz HM, et al. Are inflammatory and coagulation biomarkers related to sleep characteristics in mid-life

women?: Study of Women's Health across the Nation sleep study. Sleep. 2010;33(12):1649–1655. Epub 2010/ 12/02. PubMed PMID: 21120127; PubMed Central PMCID: PMC2982735.
77. Patel SR, Zhu X, Storfer-Isser A, et al. Sleep duration and biomarkers of inflammation. Sleep. 2009;32(2):200–204. Epub 2009/ 02/26. PubMed PMID: 19238807; PubMed Central PMCID: PMC2635584.
78. Montesi SB, Bajwa EK, Malhotra A.Biomarkers of sleep apnea. Chest.2012;142(1):239–245;Epub 2012/ 07/17. PubMed PMID: 22796846; PubMed Central PMCID: PMC3418859;
79. Nadeem R, Molnar J, Madbouly EM, et al. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med. 2013;9(10):1003–1012. Epub 2013/ 10/16. PubMed PMID: 24127144; PubMed Central PMCID: PMC3778171.
80. de Lima FF, Mazzotti DR, Tufik S, et al.The role inflammatory response genes in obstructive sleep apnea syndrome: a review. Sleep Breath.2016;20(1):331–338. Epub 2015/ 07/24. PubMed PMID: 26201496;
81. Xie X, Pan L, Ren D, et al.Effects of continuous positive airway pressure therapy on systemic inflammation in obstructive sleep apnea: a meta-analysis.Sleep Med.2013;14(11):1139–1150;Epub 2013/ 09/24. PubMed PMID: 24054505;
82. Arismendi E, Rivas E, Agusti A, et al. The systemic inflammome of severe obesity before and after bariatric surgery. PLoS One. 2014;9(9):e107859. Epub 2014/ 09/23. PubMed PMID: 25238542; PubMed Central PMCID: PMC4169608.
83. Bhushan B, Guleria R, Misra A, et al.Obstructive sleep apnoea correlates with C-reactive protein in obese Asian Indians.Nutr Metab Cardiovasc Dis.2009;19(3):184–189. Epub 2008/ 09/23. PubMed PMID: 18805681;
84. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation. 2002;105(21):2462–2464. Epub 2002/ 05/30. PubMed PMID: 12034649.
85. Arnardottir ES, Maislin G, Schwab RJ, et al. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic sleep apnea cohort. Sleep. 2012;35(7):921–932. Epub 2012/ 07/04. PubMed PMID: 22754038; PubMed Central PMCID: PMCPMC3369227.
86. Liu R, Liu X, Zee PC, et al. Association between sleep quality and C-reactive protein: results from national health and nutrition examination survey, 2005-2008. PLoS One. 2014;9(3):e92607. Epub 2014/ 03/26. PubMed PMID: 24663098; PubMed Central PMCID: PMC3963926.
87. Guilleminault C, Kirisoglu C, Ohayon MM. C-reactive protein and sleep-disordered breathing. Sleep. Epub 2005/ 02/03. PubMed PMID: 15683141 2004;27(8):1507–1511.
88. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 2004;43(4):678–683. Epub 2004/ 02/21. PubMed PMID: 14975482.
89. Gozal D, Serpero LD, Kheirandish-Gozal L, et al. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. Sleep. 2010;33(3):319–325. Epub 2010/ 03/27. PubMed PMID: 20337189; PubMed Central PMCID: PMC2831425
90. Kaushal N, Ramesh V, Gozal D.TNF-alpha and temporal changes in sleep architecture in mice exposed to sleep fragmentation.PLoS One.2012;7(9):e45610;Epub 2012/ 10/03. PubMed PMID: 23029133; PubMed Central PMCID: PMC3448632.
91. Kataoka T, Enomoto F, Kim R, et al. The effect of surgical treatment of obstructive sleep apnea syndrome on the plasma TNF-alpha levels. Tohoku J Exp Med. 2004;204(4):267–272. Epub 2004/ 12/02. PubMed PMID: 15572852.
92. Bhushan B, Guleria R, Misra A, et al.TNF-alpha gene polymorphism and TNF-alpha levels in obese Asian Indians with obstructive sleep apnea.Respir Med.2009;103(3):386–392;Epub 2008/ 11/22. PubMed PMID: 19022640.
93. Carpagnano GE, Spanevello A, Sabato R, et al. Systemic and airway inflammation in sleep apnea and obesity: the role of ICAM-1 and IL-8. Transl Res. 2010;155(1):35–43. Epub 2009/ 12/17. PubMed PMID: 20004360.
94. Ohga E, Tomita T, Wada H, et al. Effects of obstructive sleep apnea on circulating ICAM-1, IL-8, and MCP-1. J Appl Physiol. (1985). 2003;94(1):179–184. Epub 2002/ 10/23. PubMed PMID: 12391099.
95. McNicholas WT.Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease.Am J Respir Crit Care Med.2009;180(8):692–700. Epub 2009/ 07/25. PubMed PMID: 19628778
96. Wang Y, Hu K, Liu K, et al. Obstructive sleep apnea exacerbates airway inflammation in patients with chronic obstructive pulmonary disease. Sleep Med. 2015;16(9):1123–1130. Epub 2015/ 08/25. PubMed PMID: 26298789.
97. Puig F, Rico F, Almendros I, et al. Vibration enhances interleukin-8 release in a cell model of snoring-induced airway inflammation. Sleep. 2005;28(10):1312–1316. Epub 2005/ 11/22. PubMed PMID: 16295217.
98. Pákó J, Kunos L, Mészáros M, et al. Decreased levels of anti-aging klotho in obstructive sleep apnea. Rejuvenation Res. 2020;23(3):256–261.
99. Kunos L, Horvath P, Kis A, et al. Circulating survivin levels in obstructive sleep apnoea. Lung. 2018;196(4):417–424.
100. Liguori C, Romigi A, Izzi F, et al. Continuous positive airway pressure treatment increases serum vitamin D levels in male patients with obstructive sleep apnea. J Clin Sleep Med. 2015;11(6):603–607.
101. Steffanina A, Proietti L, Antonaglia C, et al. The plasminogen system and transforming growth factor-β in subjects with obstructive sleep apnea syndrome: effects of CPAP treatment. Respir Care. 2015;60(11):1643–1651.
102. Li Y, Chongsuvivatwong V, Geater A, et al. Exhaled breath condensate cytokine level as a diagnostic tool for obstructive sleep apnea syndrome. Sleep Med. 2009;10(1):95–103.
103. Dragonieri S, Porcelli F, Longobardi F, et al. An electronic nose in the discrimination of obese patients with and without obstructive sleep apnoea. J Breath Res. 2015;9(2):26005.
104. Kunos L, Bikov A, Lazar Z, et al. Evening and morning exhaled volatile compound patterns are different in obstructive sleep apnoea assessed with electronic nose. Sleep Breath. 2015;19(1):247–253.
105. Khurana S, Kumar S, Guleria R, et al. Molecular signatures of microRNA in obesity associated obstructive sleep apnea in middle-aged adults. Int J Med Res Health Sci. 2019;8(11):57–66.
106. Khurana S, Sharda S, Saha B, et al.Canvassing the aetiology, prognosis and molecular signatures of obstructive sleep apnoea. Biomarkers.2019;24(1):1–16;Epub 2018/ 08/22. PubMed PMID: 30126309.
107. Li K, Chen Z, Qin Y, et al. MiR-664a-3p expression in patients with obstructive sleep apnea: a potential marker of atherosclerosis. Medicine (Baltimore). 2018;97(6):e9813. Epub 2018/ 02/09. 10.1097/MD.0000000000009813 00005792-201802090-00021 [pii]. PubMed PMID: 29419680; PubMed Central PMCID: PMC5944670.
108. An Z, Wang D, Yang G, et al.Role of microRNA-130a in the pathogeneses of obstructive sleep apnea hypopnea syndrome-associated pulmonary hypertension by targeting the GAX gene.Medicine (Baltimore).2017;96(20):e6746. Epub 2017/05/18. PubMed PMID: 28514291; PubMed Central PMCID: PMC5440128.
109. Santamaria-Martos F, Benitez I, Ortega F, et al. Circulating microRNA profile as a potential biomarker for obstructive sleep apnea diagnosis. Sci Rep. 2019;9(1):13456. Epub 2019/ 09/19. PubMed PMID: 31530881; PubMed Central PMCID: PMCPMC6748919.
110. Freitas LS, Silveira AC, Martins FC, et al. Severe obstructive sleep apnea is associated with circulating microRNAs related to heart failure, myocardial ischemia, and cancer proliferation. Sleep Breath. 2020;24(4):1463–1472. Epub 2020/ 01/04. PubMed PMID: 31898194.
111. Khurana S, Waidha K, Guleria R, et al. In-silico investigations on selective miRNA-gene targets and their validation studies in OSA patient cohorts. Comput Biol Chem. 2020;87:107264.

112. Sharifi S, Daghighi S, Motazacker M, et al. Superparamagnetic iron oxide nanoparticles alter expression of obesity and T2D-associated risk genes in human adipocytes. Sci Rep. 2013;3(1):1–12.
113. Thovhogi N, Sibuyi NRS, Onani MO, et al. Peptide-functionalized quantum dots for potential applications in the imaging and treatment of obesity. Int J Nanomed. 2018;13:2551.
114. Weaver EM, Woodson BT, Steward DL.Polysomnography indexes are discordant with quality of life, symptoms, and reaction times in sleep apnea patients.Otolaryngol Head Neck Surg.2005;132(2):255–262;Epub 2005/ 02/05. PubMed PMID: 15692538;
115. Kainulainen S, Toyras J, Oksenberg A, et al. Severity of desaturations reflects OSA-related daytime sleepiness better than AHI. J Clin Sleep Med. 2019;15(8):1135–1142. Epub 2019/ 09/05. PubMed PMID: 31482835; PubMed Central PMCID: PMCPMC6707054.
116. Singh RD, Shandilya R, Bhargava A, et al. Quantum dot based nanobiosensors for detection of circulating cell free miRNAs in lung carcinogenesis: from biology to clinical translation. Front Genet. 2018;9:616.
117. Goldstein CA, Berry RB, Kent DT, et al. Artificial intelligence in sleep medicine: background and implications for clinicians. J Clin Sleep Med. 2020;16(4):609–618.
118. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. Ther Adv Chronic Dis. 2015;6(5):273–285.
119. (AASM) AAoSM. Clinical practice guideline on use of PAP therapy for sleep apnea.
120. (NICE) NIoHaCE. Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. 2008.
121. Patel SR, White DP, Malhotra A, et al. Continuous positive airway pressure therapy for treating gess in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Internal Med. 2003;163(5):565–571.
122. Pamidi S, Chapotot F, Wroblewski K, et al. Optimal continuous positive airway pressure treatment of obstructive sleep apnea reduces daytime resting heart rate in prediabetes: a randomized controlled study. J Am Heart Assoc. 2020;9(19):e016871.
123. Malik JA, Masoodi SR, Shoib S. Obstructive sleep apnea in Type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control. Indian J Endocrinol Metab. 2017;21(1):106.
124. Lam IPMS, Chan L-y B, Zheng L, et al. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med. 2000;162(6):2166–2171.
125. Chen L, Pei J-H, Chen H-M. Effects of continuous positive airway pressure treatment on glycaemic control and insulin sensitivity in patients with obstructive sleep apnoea and type 2 diabetes: a meta-analysis. Arch Med Sci. 2014;10(4):637.
126. Bikov A, Kunos L, Pállinger É, et al. Diurnal variation of circulating microvesicles is associated with the severity of obstructive sleep apnoea. Sleep Breath. 2017;21(3):595–600.
127. Abud R, Salgueiro M, Drake L, et al. Efficacy of continuous positive airway pressure (CPAP) preventing type 2 diabetes mellitus in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and insulin resistance: a systematic review and meta-analysis. Sleep Med. 2019;62:14–21.
128. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. J Appl Physiol. 2005;99(4):1592–1599.
129. Beebe DW, Miller N, Kirk S, et al. The association between obstructive sleep apnea and dietary choices among obese individuals during middle to late childhood. Sleep Med. 2011;12(8):797–799.
130. Johansson K, Neovius M, Lagerros YT, et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: a randomised controlled trial. Bmj. 2009;339(dec03 1):b4609.
131. Society AT. Losing weight can cure obstructive sleep apnea in overweight patients, study shows. ScienceDaily. 2009.
132. Papandreou C, Schiza SE, Bouloukaki I, et al. Effect of mediterranean diet versus prudent diet combined with physical activity on OSAS: a randomised trial. Eur Respir J. 2012;39(6):1398–1404.
133. Hudgel DW, Patel SR, Ahasic AM, et al. The role of weight management in the treatment of adult obstructive sleep apnea. an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2018;198(6):e70–e87.
134. Holty J-EC, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. Med Clinics. 2010;94(3):479–515.
135. Zhan X, Li L, Wu C, et al. Effect of uvulopalatopharyngoplasty (UPPP) on atherosclerosis and cardiac functioning in obstructive sleep apnea patients. Acta Otolaryngol. 2019;139(9):793–797.
136. Seyed Resuli A, Samur H. The results of uvulopalatopharyngoplasty in patients with moderate obstructive sleep apnea syndrome having cardiac arrhythmias. Multidiscip Cardiovasc Ann. 2020;11(2). DOI: 10.5812/mca.103810.
137. Lee HM, Kim HY, Suh JD, et al. Uvulopalatopharyngoplasty reduces the incidence of cardiovascular complications caused by obstructive sleep apnea: results from the national insurance service survey 2007–2014. Sleep Med. 2018;45:11–16.
138. Mehra P, Wolford LM, editors. Surgical management of obstructive sleep apnea. Baylor University Medical Center Proceedings, 2000: Taylor & Francis.
139. Dieltjens M, and Vanderveken OM, editors. Oral appliances in obstructive sleep apnea. Healthcare. Basel, Switzerland: Multidisciplinary Digital Publishing Institute; 2019.
140. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med. 2014;10(2):215–227.
141. Sutherland K, Takaya H, Qian J, et al. Oral appliance treatment response and polysomnographic phenotypes of obstructive sleep apnea. J Clin Sleep Med. 2015;11(8):861–868.
142. De Vries GE, Wijkstra PJ, Houwerzijl EJ, et al. Cardiovascular effects of oral appliance therapy in obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev. 2018;40:55–68.
143. Lin -C-C, Wang H-Y, Chiu C-H, et al. Effect of oral appliance on endothelial function in sleep apnea. Clin Oral Investig. 2015;19(2):437–444.
144. de Vries GE, Hoekema A, Doff MH, et al. Usage of positional therapy in adults with obstructive sleep apnea. J Clin Sleep Med. 2015;11(2):131–137.
145. Srijithesh P, Aghoram R, Goel A, et al. Positional therapy for obstructive sleep apnoea. Cochrane Database Syst Rev. 2019;2019(5). DOI:10.1002/14651858.CD010990.pub2
146. Zhang J, Zhang Q, and Wang Y, et al., editors. A real-time auto-adjustable smart pillow system for sleep apnea detection and treatment. 2013 ACM/IEEE International Conference on Information Processing in Sensor Networks (IPSN), 2013: Philadelphia, PA, USA: IEEE.