https://doi.org/10.5664/jcsm.10298

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Association of alternative polysomnographic features with patient outcomes in obstructive sleep apnea: a systematic review

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Study Objectives: Polysomnograms (PSGs) collect a plethora of physiologic signals across the night. However, few of these PSG data are incorporated into standard reports, and hence, ultimately, under-utilized in clinical decision making. Recently, there has been substantial interest regarding novel alternative PSG metrics that may help to predict obstructive sleep apnea (OSA)–related outcomes better than standard PSG metrics such as the apnea-hypopnea index. We systematically review the recent literature for studies that examined the use of alternative PSG metrics in the context of OSA and their association with health outcomes.

Methods: We systematically searched EMBASE, MEDLINE, and the Cochrane Database of Systematic Reviews for studies published between 2000 and 2022 for those that reported alternative metrics derived from PSG in adults and related them to OSA-related outcomes.

Results: Of the 186 initial studies identified by the original search, data from 31 studies were ultimately included in the final analysis. Numerous metrics were identified that were significantly related to a broad range of outcomes. We categorized the outcomes into 2 main subgroups: (1) cardiovascular/metabolic outcomes and mortality and (2) cognitive function– and vigilance-related outcomes. Four general categories of alternative metrics were identified based on signals analyzed: autonomic/hemodynamic metrics, electroencephalographic metrics, oximetric metrics, and respiratory event–related metrics.

Conclusions: We have summarized the current landscape of literature for alternative PSG metrics relating to risk prediction in OSA. Although promising, further prospective observational studies are needed to verify findings from other cohorts, and to assess the clinical utility of these metrics.

Keywords: alternative metrics, sleep apnea, apnea-hypopnea index, outcomes, polysomnogram

Citation: Hajipour M, Baumann B, Azarbarzin A, et al. Association of alternative polysomnographic features with patient outcomes in obstructive sleep apnea: a systematic review. *J Clin Sleep Med*. 2023;19(2):225–242.

BRIEF SUMMARY

Current Knowledge/Study Rationale: There is a need to identify which patients with obstructive sleep apnea (OSA) are at greater risk of adverse outcomes. Novel alternative metrics derived from the polysomnogram (PSG) may help to risk-stratify patients and provide a more nuanced description of their disease.

Study Impact: In this systematic review, we have summarized the current landscape for alternative PSG metrics relating to risk prediction in OSA. We identified many alternative metrics that could be promising; these included autonomic/hemodynamic metrics, electroencephalogram-related metrics, oximetry metrics, and respiratory event–related metrics.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common respiratory disease that affects approximately 1 billion adults worldwide.[1] OSA is associated with multiple adverse outcomes, including daytime sleepiness, reduced quality of life, motor vehicle crashes, occupational injuries, hypertension, cancer, cardiovascular disease (CVD), arrhythmias, kidney disease, cognitive dysfunction (dementia), and all-cause mortality.[2]

When OSA is suspected, patients often undergo a polysomnogram (PSG), an overnight sleep study in which a plethora of raw physiologic data are continuously collected including electroencephalography (EEG), electrocardiogram (ECG), oxygen saturation using photoplethysmography, airflow, snoring, chin/limb electromyography (EMG), eye movements, and chest wall/abdominal movements. These PSGs are scored visually by technicians to ascertain sleep stages and respiratory events. Since the 1990s, key metrics of OSA severity derived from the PSG include the apnea-hypopnea index (AHI) and simple indices of arterial desaturation such as the oxygen desaturation index (ODI) and percentage of time spent below an oxygen saturation threshold (eg, 88% or 90%).[3]

However, current PSG metrics, such as AHI, are not strongly associated with OSA-related adverse outcomes including symptoms, objective daytime function, and long-term health complications. There has thus been substantial interest in alternative PSG metrics to better quantify the severity of OSA and predict the presence or incidence of adverse OSA-related outcomes.[4] These types of metrics may thus provide the opportunity to risk-stratify patients for more aggressive therapy for OSA and other risk factors, contributing to a precision care approach. These metrics may help to select individuals who would be at increased risk of adverse outcomes (eg, cardiovascular [CV] events) who might then be preferentially recruited into randomized controlled trials.

The objective of this study was to systematically review the recent literature for studies that examined the use of alternative PSG metrics in the context of OSA and their association with health outcomes. In this context, an alternative metric was defined as one not typically reported in clinical PSG reports.

METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5]

Eligibility criteria

Inclusion criteria

Studies were included in this review if they (1) referenced an alternative metric elicited from PSG (either attended level 1 or unattended level 2), (2) reported an outcome that was patient-centered (eg, symptoms, mortality, CV outcomes), and (3) were published in the English language as full papers (ie, not as abstracts).

Exclusion criteria

Studies were excluded if they (1) referenced metrics that are typically reported from PSG (eg, AHI, rapid eye movement [REM]/non-REM [NREM] AHI, ODI, lowest oxygen saturation, arousal index, standard sleep architecture), (2) did not derive data from full PSG studies (eg, used level 3 studies or oximetry), (3) focused on pediatric patients, (4) focused on narrow populations (eg, spinal cord injuries, pregnant women, underlying lung disease), and (5) only compared the metric(s) to AHI without patient-specific outcomes. We also excluded studies that focused on advanced OSA physiologic endotyping (eg, arousal threshold, loop gain) as these are currently challenging to measure from PSG and were felt to be beyond the scope of this review.[6,7] Moreover, we excluded studies that assessed the role of therapy (continuous positive airway pressure [CPAP]) on health outcomes.

Search strategy and selection criteria

We systematically searched EMBASE, MEDLINE, and the Cochrane Database of Systematic Reviews from January 1, 2000, to April 1, 2022, using a broad search strategy and included keywords such as "obstructive sleep apnea" AND "polysomnogram" with alternative metrics. Details of the search strategy are presented in **Table S1** in the supplemental material. We limited the search to the above dates to reflect modern OSA diagnostic practices. Potentially relevant articles were accessed for full-text review. Citations from eligible articles were also searched to identify other potentially relevant studies. A flow chart of identified studies is presented in **Figure 1**.

Three authors (M.H., B.B., and N.T.A.) conducted the literature search and extracted the data. The search strategy and items for data extraction were predefined and agreed upon by the authors. Variables that were extracted from each study included the following: year of publication, country of study, data sources, the metric used, mean AHI, mean body mass index (BMI), sex breakdown, mean age, study endpoints, sample size, and major results.

RESULTS

Study selection

A total of 387 articles were identified. After duplicates were removed, 186 papers remained. Of the 186 unique studies identified in our search, 100 qualified for full-text review, of which 31 were included in the final data extraction (see **Figure 1**). The extracted data from these 31 studies are described in **Table 1**, **Table 2**, **Table 3**, and **Table 4**. Of the 31 papers included in the final review, 12 were from the United States, 5 from Australia, and the remaining countries of origin varied with representation from Finland, France, Sweden, Switzerland, Singapore, Germany, Spain, China, and Saudi Arabia. The sample size ranged from 40 participants[54] to 8,001 participants.[33] Additionally, JBI (Joanna Briggs Institute) checklists for analytical cross-sectional and cohort studies were used to further evaluate the studies.[8] All studies met the components of checklists, except for 1 study in which the authors did not control the analysis for the confounders.[46]

Identification of alternative metrics

Of the 31 studies included in the extraction, we categorized the outcomes into 2 main subgroups (ie, 1) CV/metabolic outcomes and mortality, 2) cognitive function– and vigilance-related outcomes). Metrics were also grouped into 4 categories based on the signals used from PSG (autonomic/hemodynamic metrics, EEG-related metrics, oximetry metrics, and respiratory event-related metrics: see **Table 1**, **Table 2**, **Table 3**, and **Table 4**). In each group of outcomes, we described each metric based on its category.

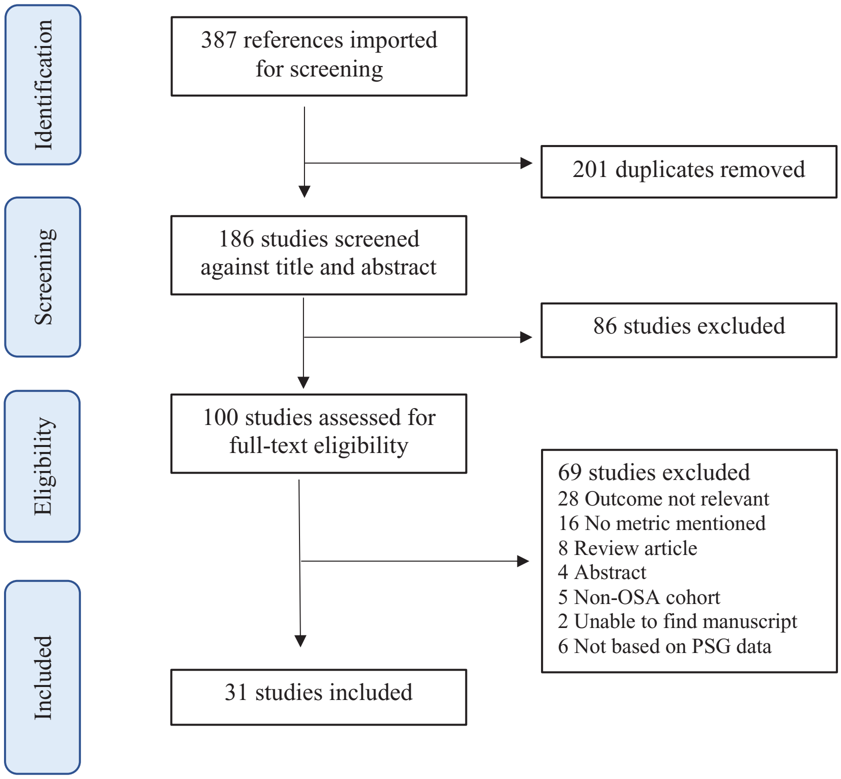
Cardiovascular/metabolic outcomes and mortality

Twenty-six studies reported CV/metabolic outcomes and mortality in patients with OSA. From these studies, 11 investigated autonomic/hemodynamic metrics, 11 studies investigated oximetric metrics, and 5 studies reported EEG metrics and respiratory-related metrics.

Autonomic/hemodynamic metrics: 11 studies

These metrics were derived from pulse oximetry (photoplethysmography [PPG]) for estimating blood pressure (BP) changes

Figure 1—PRISMA flow chart of identified studies, excluded and included.



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

and heart rate variability (HRV) or derived from ECG signals combined with respiratory data. Five unique CV-related metrics were described (see **Table 1**).

Heart rate response to respiratory events

Elevated heart rate response to respiratory events ("ΔHR") was recently introduced by Azarbarzin and colleagues.[9] This metric was shown to be associated with deleterious CV outcomes in patients with OSA.[9] The risk was exclusively observed in individuals with no excessive daytime sleepiness. Activation of sympathetic activity is associated with an increase in the heart rate, the magnitude of which may also be affected by the severity of respiratory events,[10] the intensity of cortical arousal,[11] and the responsiveness of the autonomic nervous system.[12] Therefore, it is plausible that the OSA-specific heart rate response may reflect important aspects of the autonomic response to respiratory events, useful to predict CV and metabolic outcomes. The ΔHR was defined as the difference between a maximum pulse rate (derived from the oximetry signal) during a subject-specific search window and the minimum pulse rate during apneas and hypopneas. Individuals with OSA who demonstrated an elevated ΔHR were at increased risk of nonfatal and fatal CVD and all-cause mortality (hazard ratio [95% confidence interval] = 1.60 [1.28–2.00], 1.68 [1.22–2.30], and 1.29 [1.07–1.55], respectively) in the Sleep Heart Health Study (SHHS). Of note, this cohort predominantly included middle-aged or older individuals (mean age = 64.2 ± 11 years). Further studies are needed to prospectively replicate these findings in younger individuals.

Pulse arrival time

Another alternative metric extracted from PPG, pulse arrival time (PAT), has been a widely used surrogate of pulse transit time, and has been used to estimate BP.[13] Arterial stiffening from increased BP leads to a rise in pulse wave velocity and a fall in PAT.[13] Since nocturnal sleep BP is an important prognostic marker of CV health, PAT assessment during sleep may provide useful information related to CV health in patients with OSA. PAT is calculated from the time interval between ECG *R*-waves and the pulse wave detected by pulse oximetry. An increase in PAT is indicative of an increase in BP.[14] Kwon and colleagues[15] calculated the PAT response to respiratory events using the area under the PAT waveform (first derivate of PAT) following respiratory events. Cross-sectional analyses revealed that higher PAT response was associated with higher left ventricular mass (5.7 g/m^2 higher in the fourth compared with the first quartile, $P < .007$) and a higher carotid plaque burden score (0.37 higher in the fourth compared with the first quartile, $P = .02$). A nonsignificant association with greater odds of coronary artery calcification was also observed ($P = .06$). Finally, they showed that a 1-standard-deviation increase in average PAT response was associated with 18% higher risk of incident CVD. While these findings may help better identify high-risk individuals with OSA, further studies are needed to prospectively

Table 1—Studies assessing autonomic/hemodynamic metrics.

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Thomas (2009)[28] USA	5247/Retro of Pros	1	51.6	28.7	9.1	62.2	47.6	CPC (e-LFCNB)	CV outcomes	Elevated LFCNB, was associated with greater severity of sleep apnea and fragmented sleep. After adjustment for potential confounders, an independent association with prevalent hypertension and stroke was found.
Magnusdottir (2020)[29] USA	241/Retro of Pros	2	73	34	25.5	63	100	CPC	Nocturnal blood pressure response to CPAP	CPC-derived sleep quality impacted 24-h MAP and MDP, as well as BP during wake
Blanchard (2021)[20] France	7205/Retro of Pros	2	62.3	29	22	60	86.7	PRV	AF	PRV indices were independent predictors of AF incidence.
Azarbarzin (2021)[9] USA	5970/Retro of pros	1	MESA: 47.5 SHHS: 47.7	MESA: 28.8 SHHS: 28.3	MESA: 19.3 SHHS: 14.1	MESA: 68.5 SHHS: 64.2	MESA: 3.9 SHHS: 29	ΔHR	CV disease and all-cause mortality	In MESA, HR was associated with NT-proBNP, coronary calcium, and Framingham risk, and in SHHS, individuals with a high ΔHR were at increased risk of nonfatal/fatal CVD and all-cause mortality
Kwon (2021)[15] USA	1407/Retro of Pros	2	47.5	28.8	19.5	68.4	Not referenced	PAT response	CV outcomes	Increase in average PAT response was associated with LV mass, CPB score, CAC prevalence and 18% higher risk of incident CVD
Alomri (2022)[45] Saudi Arabia	75/Retro	1	70	33.2	Not referenced	41.1	84	SBP derived from PAT	Cognitive dysfunction (Austin Maze test)	Nocturnal peaks in SBP and difference between resting and nocturnal peaks of SBP in OSA were associated with visuospatial dysfunction, even after controlling for age, smoking status, depressive symptoms, hypoxia, and sleep fragmentation

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Table 1—Studies assessing autonomic/hemodynamic metrics. (*Continued*)

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Trzepizur (2022)[22] France	5358/Retro of Pros	2	63.66	30	27	60	100	PRV	MACEs	PRV was not associated with MACEs.
Blanchard (2021)[21] France	3597/Retro of Pros	2	63	28	20	58	85	PRV	Risk of stroke incidence	Nighttime sympathetic/ parasympathetic tone (PRV) was associated with stroke risk.
Hirotsu (2020)[16] Switzerland	2162/Cross-sectional	2	49	26.2	Not referenced	57	Not referenced	PWA	Hypertension, diabetes, and CV event	Independent association of PWA-drop features (lower frequency, longer duration, and greater area under the curve) with hypertension, diabetes, and CV events
Strassberger (2021)[17] Sweden	358/Retro	1	64	30	13	55	100	CRI	CV risk	Pulse wave analysis during sleep provides a powerful approach for cardiovascular risk assessment in addition to conventional sleep study parameters
Berger (2022)[23] Switzerland	1784/Retro of Pros	1	48.2	26	Not referenced	58	Not referenced	HRV	CVD	In a fully adjusted model, AC, DC, and HRF were the only HRV metrics significantly associated with incident CVD events

AC = acceleration capacity, AF = atrial fibrillation, AHI = apnea-hypopnea index, BMI = body mass index, BP = blood pressure, CPB = carotid plaque burden, CPAP = continuous positive airway pressure, CPC = cardiopulmonary coupling, CRI = Cardiac Risk Index, CV = cardiovascular, CVD = cardiovascular disease, DC = deceleration capacity, e-LFCNB = narrow-band elevated low frequency coupling, HR = heart rate, HRV = heart rate variability, LV = Left Ventricular, MACE = major adverse cardiovascular event, MDP = mean diastolic blood pressure, MESA = Multi-Ethnic Study of Atherosclerosis, M/F = male/female, NT-proBNP = N-terminal prohormone BNP, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, PAT = pulse arrival time, Pros = prospective, PRV = pulse rate variability, PSG = polysomnography, PWA = pulse wave amplitude, Retro = retrospective, Retro of Pros = retrospective analysis of prospective study, SBP = systolic blood pressure, SHHS = Sleep Heart Health Study.

Table 2—Studies assessing EEG metrics.

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Schwartz (2006)[50] Germany	100/Cross-sectional	1	Not referenced	Not referenced	Not referenced	Not referenced	Not referenced	Arousal duration	ESS	Longer arousals correlated more strongly with ESS than the frequency or time attributable to the more numerous brief arousals.
Vakulin (2016)[49] Australia	76/Cross-sectional	1	81	32.2	29.8	42.8	100	EEG power Spectrum analysis	Driving simulator performance	Among clinical and quantitative EEG variables, significant predictors of worse steering deviation were total EEG power during NREM and REM sleep, beta EEG power in NREM and delta EEG power in REM and sleep onset latency.
Azarbarzin (2020)[46] USA	1378/Retro of Pros	1	67.6	30	22	65	100	LR-ORP	Risk of car crash	Compared to the lowest quartile of sleep depth coherence, individuals in the highest quartile had a 62% lower risk of accident.
Kim (2021)[31] USA	2055/Cross-sectional	1	46	14.8	28.7	68.4	Not referenced	ORP	Hypertension	ORP was not associated with blood pressure changes
Lechat (2021)[32] Australia	5084/Retro of Pros	1	47.3	28.1	9.9	63	Not referenced	Delta EEG power	All-cause mortality	Disrupted delta EEG power during sleep was associated with a 32% increased risk of all-cause mortality compared with no fragmentation.
Djonlagic (2021)[47] USA	3819/Retro of Pros	2	MESA:48 MrOS: 100	Not referenced	Not referenced	Not referenced	Not referenced	EEG Metrics	Cognitive performance MESA: DSCT, CASI, DSF, DSB MrOS: Trails B, 3MS, DVT	Cognitive performance was related to sleep across macro architecture and multiple spectral, spindle, SO and spindle–SO coupling domains. Associated metrics fell across at least three broad classes.

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Table 2—Studies assessing EEG metrics. (*Continued*)

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Shahrbabaki (2021)[33] Australia	8001/Retro of Pros	SHHS:1 MrOS:2 SOF:2	62.5	MrOS:27.2 SHHS:28.3 SOF:27.7	MrOS:20.1 SHHS:9.5 SOF:27.6	MrOS:76.6 SHHS: 64 SOF:82.9	Not referenced	AB	Mortality: all cause and CV	In women, AB was associated with all-cause mortality and CV mortality. In men, it was not clear (results were reverse in SHHS and MrOS)
McCloy (2021)[48] Australia	190/Retro	1	61	36.5	28.5	56	100	SBI	Vigilance	SBI used to model sleep spindle characteristics to PVT indices and the proposed model were able to detect patients with vigilance marker
Duce (2021)[51] Australia	65/Retro	1	55	31.7	26.1	53	100	Arousal duration	Cognitive outcomes	PVT impaired group had more EEG arousals greater than 5 s, 7 s, and 15 s in duration.

AB = arousal burden, AHI = apnea-hypopnea index, BMI = body mass index, CASI = Cognitive Abilities Screening Instrument, DSB = Digit Span Test (backward), DSCT = Digit Symbol Coding Test, DSF = Digit Span Test (forward), DVT = Digit Vigilance Test, EEG = electroencephalography, ESS = Epworth Sleepiness Scale, MESA = Multi-Ethnic Study of Atherosclerosis, MrOS = Osteoporotic Fractures in Men Study, NREM = non–rapid eye movement, ODI = oxygen desaturation index, ORP = odds ratio product, OSA = obstructive sleep apnea, Pros = prospective, PSG = polysomnography, PVT = Psychomotor Vigilance Test, RDI = respiratory disturbance index, REM = rapid eye movement, Retro = retrospective, Retro of Pros = retrospective analysis of prospective study, SBI = spindle burst characteristics, SD = standard deviation, SHHS = Sleep Heart Health Study, SO = slow oscillation, SOF = Study of Osteoporotic Fractures, SWA = slow-wave activity, 3MS = Mini-Mental State Examination.

Table 3—Studies assessing oximetric metrics.

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Azarbarzin (2019)[36] USA	7854/Retro of Pros	MrOS: 2 SHHS: 1	MrOS: 100 SHHS: 45.3	MrOS: 27.2 SHHS: 28.3	MrOS: 15.7 SHHS: 17.1	MrOS: 74.3 SHHS: 61.0	MrOS: 39.8 SHHS: 26	HB	CVD mortality and all-cause mortality	Individuals in the MrOS study with hypoxic burden in the highest 2 quintiles had hazard ratios of 1.81 and 2.73, respectively, compared with the first quintile for CV-related mortality. The group in the SHHS with HB in the highest quintile had a hazard ratio of 1.96 for CV-related mortality.
Azarbarzin (2020)[37] USA	7534/Retro of Pros	MrOS: 2 SHHS: 1	MrOS: 100 SHHS: 45.3	MrOS: 27.1 SHHS:28.3	MrOS: 11.4 SHHS: 8.6	MrOS: 76.2 SHHS: 63.6	Not referenced	HB	HF	The sleep HB was associated with incident HF in men in 2 independent cohorts. Moreover, HB predicted incident HF in groups with both high and low AHI levels.
Azarbarzin (2021)[9] USA	5970/Retro of Pros	1	MESA: 47.5 SHHS: 47.7	MESA: 28.8 SHHS: 28.3	MESA: 19.3 SHHS: 14.1	MESA: 68.5 SHHS: 64.2	MESA: 3.9 SHHS: 28	HB	CVD and all-cause mortality	Relationship between delta HR and fatal CVD or all-cause mortality was strengthened in patients with a high HB. They also noted no association between a high delta HR and fatal CVD or all-cause mortality in those with a low HB.
Jackson (2021)[38] USA	1895/Retro of Pros	2	46.3	28.8	Not referenced	68.2	Not referenced	HB	Chronic kidney disease	ASHB was associated with moderate-to-severe CKD. Black women in highest vs lowest quantile of ASHB also had a higher CKD prevalence.
Kim (2021)[31] USA	2055/Cross-sectional	1	46/54	28.7	14.8	68.4	Not referenced	HB	Hypertension	Higher burden was associated with higher BP.

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Table 3—Studies assessing oximetric metrics. (*Continued*)

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Trzepizur (2022)[22] France	5358/Retro of Pros	2	63.66/36.34	30	27	60	200	HB	MACE	HB was an independent predictor of incident CV events and death.
Blanchard (2021)[21] France	3597/Retro of Pros	2	63	28	20	58	85	HB	Risk of stroke incidence	HB was associated with stroke risk in OSA patients.
de Chazal (2021)[39] Australia	4686/Retro of Pros	2	48/52	Not referenced	Not referenced	>40	Not referenced	REDTA	CVD mortality	Hazard ratios in adjusted Cox analysis for predicting cardiovascular death using REDTA are up to 1.90 in the third quantile.
Wang (2020)[41] China	102/Cross-sectional	1	67/33	29.5	63	100	50.3	ODR	Hypertension	ODR was more strongly associated with elevation of BP and BPV in patients with severe OSA
Kwon (2021)[42] USA	2631/Retro of Pros	2	100/0	27.2	18	76.4	Not referenced	LFCt	CVD and all-cause mortality	LFCt was independently associated with both CV and all-cause mortality in older men with SDB, independent of both baseline CV burden and conventional SDB metrics.
Kainulainen (2020)[52] Finland	743/Retro	1	58.7	35.1	23.7	56.8	100	Desaturation severity, obstruction severity, respiratory event duration	PVT reaction time and the number of lapses	Desaturation severity is significantly associated with increased risk of impaired PVT performance.
Muraja-Murro (2013)[43] Finland	226/Retro	1	Not referenced	29.3	19.5	54.6	38.8	Desaturation severity, obstruction severity, respiratory event duration	Mortality	Obstruction severity was the only parameter which was related statistically significantly to mortality in the severe OSA category

AHI = apnea-hypopnea index, BMI = body mass index, BP = blood pressure, BPV = blood pressure variability, CKD = chronic kidney disease, CV = cardiovascular, CVD = cardiovascular disease, HB = hypoxic burden, HF = heart failure, HR = heart rate, LFCt = lung to finger circulation time, MACE = major adverse cardiovascular event, MESA = Multi-Ethnic Study of Atherosclerosis, MrOS = Osteoporotic Fractures in Men Study, ODI = oxygen desaturation index, ODR = oxygen desaturation rate, OSA = obstructive sleep apnea, Pros = prospective, PSG = polysomnography, PVT = Psychomotor Vigilance Test, REDTA = Respiratory Event Desaturation Transient Area, Retro = retrospective, Retro of Pros = retrospective analysis of prospective study, SD = standard deviation, SDB = sleep-disordered breathing, SHHS = Sleep Heart Health Study.

Table 4—Studies assessing respiratory event–related metrics.

Study	Study Size/ Type	Type of PSG (Level 1 or 2)	Sex (% male)	Mean BMI (kg/m^2)	Mean AHI (/h)	Mean Age (years)	% OSA Participants	Metric	Outcome	Results
Goh (2018)[53] Singapore	821/Retro	1	67	28	28	48	100	Apneic and Hypopneic load	ESS	Linear regression analysis found age (P < .001), apnea load (P = .005), REM (P = .021) and stage 1 sleep duration (P = .042) were independent factors correlated to ESS.
Butler (2019)[44] USA	5712/Retro of Pros	1	48	28.1	13.8	63.3	67	Respiratory event duration	All-cause mortality	Individuals with the shortest-duration events had a significantly increased hazard ratio for all-cause mortality
Kim (2021)[31] USA	2055/Cross-sectional	1	46	28.7	14.8	68.4	Not referenced	Duty cycle and IFL	Hypertension	Higher duty cycle and IFL were associated with lower BP
Mediano (2007)[54] Spain	40/Retro	1	100	32	61	50	100	Apnea duration	EDS	Longer apnea duration can be a determinant of excessive daytime sleepiness in OSA patients

AHI = apnea hypopnea index, BMI = body mass index, BP = blood pressure, EDS = excessive daytime sleepiness, ESS = Epworth Sleepiness Scale, IFL = inspiratory flow limitation, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, Pros = prospective, PSG = polysomnography, RDI = respiratory disturbance index, REM = rapid eye movement, Retro = Retrospective, Retro of Pros = retrospective analysis of prospective study, SD = standard deviation.

confirm them in younger individuals. Furthermore, the calculation of PAT requires more sophisticated signal processing techniques that may hinder its utility in routine clinical care.

Pulse wave characteristics

In a study in 2020, Hirotsu and colleagues[16] examined the clinical significance of pulse wave amplitude (PWA) drops, extracted from PPG signal during sleep, as a biomarker for cardiometabolic disorders. The amplitude of the PPG signal was considered as a surrogate of the PWA. PWA variations seem to be proportional to the sympathetic outflow directed to the vessels, reflecting sympathovagal balance. Thus, they hypothesized that PWA-drop features during sleep would be independently associated with hypertension, diabetes, and previous CV events as these conditions are associated with impairments in the autonomic nervous system and vascular function. After preprocessing of PPG signal and derivation of peaks and nadirs, time course and first derivate of PWA-variation were extracted. PWA-drops with an amplitude > 30% and a duration > 4 heart beats, their frequency, duration, and area under the curve (AUC) were calculated. They showed that lower PWA-drop index, longer duration, and greater AUC were associated with increased risk of hypertension, diabetes, or CV events. Participants in the lowest quartile compared with those in the highest quartile of mean duration-normalized PWA-drop index had a significantly higher odds ratio (OR) of hypertension (OR = 1.60 [1.19–2.16]), CV event (OR = 3.26 [1.33–8.03]), and diabetes (OR = 1.71 [1.06–2.76]). Similar results were reported for mean duration- and mean AUC-normalized PWA-drop indexes. In another study by Strassberger and colleagues,[17] a novel cardiac risk index (CRI) was computed based on pulse wave signals derived from pulse oximetry, reflecting vascular stiffness, cardiac variability, vascular autonomic tone, and nocturnal hypoxia. CRI calculated using an algorithm that computed 9 parameters (pulse index, oxygen saturation [SpO_2] index, PWA index, respiratory-related pulse oscillations, pulse propagation time, periodic and symmetric desaturations, time under 90% SpO_2, difference between pulse and SpO_2 index, and arrhythmia) from PPG signal.[18] They showed that CRI but not AHI or ODI significantly increased the area under the receiver operating characteristic curve (AUC) after controlling for confounders. Moreover, comparison of the ODI and CRI indicated only the novel risk index had an independent influence on CV risk prediction.

Both studies revealed the benefits of PPG-derived metrics to predict cardiometabolic outcomes. However, the mean age of participants in both studies was younger in comparison to most of the studies, and investigation of these metrics on prospective cohorts with different characteristics would be essential.

Pulse rate variability/HRV

HRV is a noninvasive tool for the assessment of autonomic nervous activity. Pulse rate variability (PRV) derived from nocturnal pulse oximetry can provide a measurement of HRV during sleep.[19] This specific metric was studied by Blanchard and colleagues[20] to assess the association between PRV and the onset of atrial fibrillation (AF) in patients with suspected OSA. After artifact removal, pulse-to-pulse intervals were calculated by identifying local peaks (*R*-waves). Normal-to-normal (NN) beat intervals (intervals between normal *R*-peaks), the standard deviation (SD) of NN intervals (SDNN), and the root mean square of the successive NN differences (RMSSD) were calculated. Higher PRV, as assessed by SDNN and RMSSD, and a lower ratio of low-frequency and high-frequency PRV (a measure of sympathetic to parasympathetic autonomic balance) were associated with a higher risk of AF. The association remained highly significant after adjusting for confounders. Finally, they showed that patients with the highest quartile of T90 (the percentage of recording time with oxygen saturation < 90%) and RMSSD had a lower AF survival than those with only 1 or neither of these conditions. Blanchard and colleagues[21] in another large multicenter, clinic-based cohort investigated if these PSG-derived indices of HRV could predict stroke incidence. They showed that patients with lower ratio of low-frequency and high-frequency PRV were at higher risk of stroke after adjusting for confounding risk factors and positive airway pressure adherence. A 1-unit increase in log-transformed low frequency (LF):high frequency (HF) ratio was associated with a 44% decrease in stroke risk. The association was stronger in patients aged more than 60 years. However, stroke incidence was more strongly associated with HF PRV among nonobese individuals compared with those with obesity. Recently, Trzepizur and colleagues[22] tested PRV on a cohort from France to examine its association with major adverse CV events (MACEs). Log-transformed PRV indices (ln SDNN, ln LF, ln HF, and ln LF-to-HF ratio) were found to be associated with incident MACEs in unadjusted models, but the association weakened and became nonsignificant after adjusting for confounders. Finally, Berger and his colleagues[23] assessed the association between nocturnal HRV and CVD incidence over 4 years in a population-based sample. Polysomnography-based ECGs were exported to analyze time- and frequency-domain HRV, Poincaré plots indices, detrended fluctuation analysis, acceleration capacity (AC) and deceleration capacity (DC), entropy, heart rate fragmentation, and heart rate turbulence.

To distinguish between vagal and sympathetic factors that affect HRV, they used a signal processing algorithm to separately characterize deceleration and acceleration of heart rate. Heartbeat intervals longer than the preceding interval are identified as DC and, for computation of AC, heartbeat intervals shorter than the preceding interval are identified as AC.[24] They showed that nocturnal novel HRV parameters (eg, AC, DC, and heart rate fragmentation) were better predictors of CVD events than traditional HRV parameters (eg, SDNN, RMSSD, HF). In a fully adjusted model, AC (hazard ratio per 1-SD increase [95% confidence interval] = 1.59 [1.17–2.16]; P = .004), DC (0.63 [0.47–0.84], P = .002), and heart rate fragmentation (1.41 [1.11–1.78], P = 0.005) were the only features significantly associated with incidence of CVD events.

Considering the results of these 4 studies that investigated HRV-related indices to predict CV/metabolic outcomes and mortality, it seems that the metrics (eg, HF, LF, RMSSD) that were associated with outcomes in 1 study did not persist in other studies. Therefore, more investigations on HRV-related metrics need to be done to derive a reliable metric associated with this group of metrics. The other reported issues with HRV in sleep-related studies are the assumption of stationarity of this signal, which is not true in sleep apnea, and the complexity of HRV calculation.[25,26]

Cardiopulmonary coupling

Cardiopulmonary coupling (CPC) is an ECG-based metric designed to combine information from HRV and ECG-derived respiration.[27] Briefly, this method proposed to characterize sleep stability using a continuous single-channel ECG, by mathematically combining QRS wave amplitude fluctuations that are related to the mechanical effects of respiration with HRV changes that are associated with neuro-autonomic tone modulation. Thomas and colleagues,[28] using the data from the SHHS cohort, found that an ECG-derived spectrographic marker related to LF CPC (narrow-band elevated LF) was associated with greater sleep apnea severity. This narrow-band elevated LF coupling was also associated with prevalent hypertension and stroke (OR [95% confidence interval] = 1.02 [1.01–1.04], P = .001, and 1.65 [1.19–2.29], P = .003, respectively), after adjustment for potential confounders. In 2020, Magnusdottir and colleagues[29] examined if changes in objective sleep quality index assessed through cardiopulmonary-coupling analysis impacted BP in patients with OSA at high-CV risk. The sleep quality index metric consists of a measure of sleep stability as stable sleep (HF coupling), unstable sleep (LF coupling), sleep fragmentation (elevated LF coupling broad-band), and a marker of periodic breathing (periodicity, elevated LF coupling narrow-band). The sleep quality index was presented on a scale of 0 to 100 in which a higher number represented a better quality of sleep. They found that CPAP therapy significantly improved BP, with improvement in mean arterial BP during sleep (MAP Sleep) when compared with nocturnal supplemental oxygen therapy or healthy lifestyle and sleep education therapy. They also showed that sleep quality impacted 24-hour mean arterial pressure, mean diastolic BP, and BP during wakefulness. Elevated LF coupling derived from CPC analysis was investigated in 2 cohorts with different characteristics (eg, mean age, sex, PSG type). The results showed this metric could be useful to predict cardiometabolic outcomes in patients with OSA.

EEG metrics; 3 studies

More in-depth analysis of EEG may provide new insights into how OSA is associated with health outcomes. These studies used metrics derived from EEG spectral analyses, spindle morphology, and arousal duration. Out of 9 studies that reported EEG metrics, 3 of them investigated the association between EEG metrics and CV/metabolic outcomes and mortality and the rest reported cognitive function– and vigilance-related outcomes (see **Table 2**).

Odds ratio product

OSA reduces overall sleep depth because of frequent respiratory events and arousals. Poor quality sleep and excessive wake time have been independently associated with hypertension.[31] Odds ratio product (ORP) is a proprietary metric that quantifies sleep depth based on quantitative analysis of the EEG power spectra. ORP ranges from 0 to 2.5, with lower values indicative of deeper sleep.[30] Kim and colleagues[31] examined the association of ORP with BP in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort; they showed that higher ORP was not significantly associated with BP in unadjusted or adjusted models.

EEG power

Delta wave activity is a key feature of deep sleep. Therefore, overnight power spectral analysis of delta activity might be a useful measure of sleep disturbance. Disrupted sleep could, in turn, affect cardiometabolic activity. Lechat and colleagues[32] investigated whether power spectral measures and spectral entropy-based markers of delta wave activity (0.5 to 4.5 Hz) during sleep predicted mortality stronger than conventional sleep quality and disturbance metrics, including wake after sleep onset, arousal index, and average power across EEG frequency bands. The degree of uniformity of the delta wave density function was quantified using spectral entropy. The spectral entropy was computed by calculating the Shannon entropy of the power spectrum of the delta wave density function. A higher spectral entropy (higher frequency fluctuations in delta power) and a lower spectral entropy (short or absent delta power activity fluctuations) of EEG delta power (ie, the upper and lower tertiles of entropy distribution function) during sleep were associated with a 32% increased risk of all-cause mortality compared with the mid-tertile of the entropy distribution function, after adjusting for total sleep time and other clinical-related covariates including sleep apnea. This association was of a similar magnitude to a reduction in total sleep time from 6.5 hours to 4.25 hours. In addition to replication of these findings across different age- and sex-specific groups, future studies are needed to determine the associations of delta wave entropy with subjective and objective measures of daytime sleepiness and symptoms.

Arousal burden

Arousals impact heart rate, BP, and cardiac hemodynamics may also disrupt the circadian rhythm of the CV system, which is associated with unfavorable metabolic outcomes, such as higher BP. Shahrbabaki and colleagues[33] studied arousal burden (AB; total duration of arousals normalized by total sleep time) to predict the risk of cardiac events and all-cause mortality. For women from the SHHS, and the Study of Osteoporotic Fractures (SOF) there was a correlation between AB and CV-related and all-cause mortality. For men, the link between AB and mortality was not clear. The association for men could not be reproduced in both cohorts. For example, in the SHHS, AB was only associated with all-cause mortality; however, in the Osteoporotic Fractures in Men Study (MrOS), AB was associated with CV mortality but not all-cause mortality (all-cause mortality—MrOS: HR = 1.11, P = .261; SHHS-men: HR=1.31, P = .011; CV mortality—MrOS: HR=1.35, P = .034; SHHS-men: HR=1.24, P = .271). Considering the reported results from all investigated cohorts, this metric does not appear to predict CV-related outcomes and mortality across sex-specific subgroups. Another issue with AB is that, compared with respiratory events/desaturations, arousal scoring is highly variable in the clinical and research settings and therefore it may be challenging to get an accurate measure of arousal duration.[34,35] Furthermore, developing algorithms for arousal scoring appears to be challenging.

Oximetric metrics: 11 studies

Novel metrics related to continuous oxygen saturation from overnight PSG data have been well documented. Eleven studies examined the association between oxygen saturation metrics and CV/metabolic outcomes and mortality while 7 studies considered "hypoxic burden" as a metric for their research (**Table 3**).

Hypoxic burden

Hypoxic burden (HB) in response to respiratory events (otherwise, known as sleep apnea–specific hypoxic burden) is defined as the total area under the desaturation curve from a pre–respiratory event baseline and calculated as the sum of individual burdens divided by total sleep time. Azarbarzin and colleagues[36] showed that HB strongly predicted CVD mortality (MrOS and SHHS cohorts) and all-cause mortality (only in MrOS). Patients in MrOS and SHHS cohorts with HB in the highest quintile had a hazard ratio of 2.73 ($P < .001$) and 1.96 ($P < .05$) for CV-related mortality, respectively, whereas the AHI was an unreliable predictor. In 2021, Azarbarzin's group used HB in conjunction with ΔHR changes (see autonomic/hemodynamic metrics section above) and found that the relationship between ΔHR and fatal CVD or all-cause mortality was stronger in patients with a high HB.[9] No association between a high ΔHR and fatal CVD or all-cause mortality was observed in those with a low HB. In a recent large multicenter clinical cohort of patients with OSA, Blanchard and colleagues[21] showed that patients with higher HB were at higher risk of stroke after adjusting for confounding risk factors (adjusted hazard ratio = 1.30; 95% confidence interval: 1.05–1.61; $P = .02$). However, the association was nonsignificant after exclusion of 29 patients with transient ischemic attack. Recently, Trzepizur and colleagues[22] demonstrated that HB was associated with an increased risk of MACEs or all-cause mortality. Interestingly, a stronger association between HB and MACEs was observed in women and younger patients. In another study, Azarbarzin and colleagues[37] examined the association between HB and incident heart failure in 2 independent cohorts (SHHS and MrOS). HB was associated with an increased risk for incident heart failure in men after considering demographic factors and comorbidities. Every 1-SD increase in HB was associated with an 18% and 22% increased risk of incident heart failure in SHHS and MrOS, respectively. Importantly, HB was found to predict incident heart failure in individuals with both a high and a low AHI. In addition to these longitudinal associations, HB was also shown to be associated with increased BP and chronic kidney disease (CKD) in cross-sectional analyses. In 2021, Kim and colleagues[31] assessed the associations between BP and OSA-specific HB in participants from the MESA cohort. They found that a higher HB was linked to higher blood pressure, such that for every 1-SD increase in HB there was an associated 1.1% increase in systolic and 1.9% increase in diastolic BP among those not taking hypertension medications. Finally, in the same cohort (MESA), Jackson and colleagues[38] showed a significant association between HB and CKD. Participants in the highest HB quintile (in comparison to the lowest) were at greater risk of CKD (36% significantly higher moderate-to-severe CKD prevalence ratio = 1.36 [1.00–1.86]). The prevalence of CKD was also higher in Black women in the highest vs lowest quantile of HB.

HB as a metric for evaluation of oxygen desaturation in response to respiratory events has been evaluated in different studies and cohorts. HB can be measured from home sleep tests, which is increasingly becoming popular. However, future studies are needed to demonstrate the utility of this metric in a younger population with sleep apnea and to determine its utility to predict CPAP benefit. Finally, an automated and standardized method is needed to calculate this metric from in-home and in-laboratory studies.

Respiratory event desaturation transient area

Philip de Chazal and colleagues[39] sought to develop a metric that could be used to measure hypoxemia based on the area under the oxygen saturation (SpO_2) signal without requiring estimation of pre-event baseline saturation, thereby simplifying calculation compared with HB. For each respiratory event, they calculated the area between 100% and the SpO_2 curve from midway through the event and extending for 2.5 event lengths. The respiratory event desaturation transient area (REDTA) value was then calculated by summing the areas for events and dividing by 3,600. Using the SHHS cohort, the hazard ratio in adjusted analysis for predicting CVD using REDTA was 1.71 (1.09–2.69) in the last quintile compared with the first quintile, which was similar to Azarbarzin's metric (HB).[36] In contrast to HB, a dose–response relationship between CVD mortality and REDTA was not observed as the hazard ratio in the adjusted analysis. It was highest in the third quintile and decreased for the fourth and fifth quintiles.

Oxygen desaturation rate

The oxygen saturation variations in OSA disease are cyclic drops in saturation rather than a sustained drop in oxygen saturation during sleep. HF intermittent hypoxemia characterized by cycles of hypoxemia with reoxygenation differs from sustained LF hypoxemia, which might lead to endothelial dysfunction that can further contribute to hypertension development.[40] Wang and colleagues[41] investigated the association between oxygen desaturation rate and BP in patients with OSA. The decrease in SpO_2 during apnea from the start of the desaturation to the nadir of desaturation divided by the duration of desaturation was used to calculate oxygen desaturation rate (ODR). Comparisons between the 2 groups of greater ODR vs lesser ODR showed significantly higher systolic BP values in the high-ODR group as well as short-term BP variability (event-related BP elevation) and the prevalence of hypertension. Investigating this metric on different cohorts with greater size, considering patients with mild and severe OSA, and evaluating this metric on longitudinal studies need to be done in future studies.

Lung to finger circulation time

Sleep study–derived circulation time (Ct) reflects oxygen transport time from the lung to the periphery. Long Ct is a sign of circulation delay in patients with heart failure. Therefore, prolonged Ct derived from PSG could indicate subclinical heart failure.[42] Kwon and colleagues[42] quantified lung to finger Ct (LFCt), the average time between the end of respiratory events and nadir oxygen desaturations associated with those events. LFCt was significantly associated with an increased risk for CVD and all-cause mortality; the hazard ratios for the last quartile were 1.36 (1.02–1.81), $P = .04$, and 1.35 (1.14–1.60), $P < .001$, respectively, compared with the first quartile. Even though their proposed metric was able to predict CVD and mortality in patients with OSA, evaluation of LFCt on cohorts with a lower mean age and in both men and women needs to be done. Furthermore, we do not know the extent to which this metric is related to OSA. This metric may be a marker of subclinical heart failure and, therefore, future CPAP-related studies are needed to better understand this metric.

Desaturation severity and obstructive severity

Muraja-Murro and colleagues[43] investigated the association between duration or depth of obstruction (length of apneas or hypopneas), severity of desaturation events (area of desaturation events), obstruction severity, and mortality rate. The "obstruction severity" parameter was the sum of the products of apnea and hypopnea duration and related desaturation areas normalized with the total analyzed time. They showed that the obstruction severity parameter was higher in deceased patients than in alive patients with severe OSA. In addition, the "obstruction severity" was the only parameter related to mortality in the severe OSA category based on a multivariable logistic regression analysis. Future studies are needed to prospectively validate this metric in larger, more diverse studies with longer follow-up durations.

Respiratory event–related metrics: 2 studies

Three novel respiratory event–related metrics derived from airflow/nasal pressure signals from overnight PSG data linked to CV/metabolic outcomes and mortality have been reported (**Table 4**).

Event duration

In a study by Butler and colleagues,[44] short event duration, a potential marker of reduced arousal threshold, was shown to predict all-cause mortality in the SHHS cohort. Individuals with the shortest duration of respiratory events experienced a 20% increased mortality rate compared with those with the longest events. This relationship was observed in both men and women and was strongest in those with moderate sleep apnea. Although the reported metric was able to predict mortality in SHHS patients, the physiological interpretation of how a shorter event might lead to a higher rate mortality needs further investigation. Similar to other studies, future work is needed to replicate these findings in other cohorts, including in younger individuals.

Duty cycle and inspiratory flow limitation

Kim and colleagues[31] examined the association of airflow limitation with increased BP. Airflow limitation was assessed using duty cycle (inspiratory time/total respiratory cycle time) and percentage of breaths with flow limitation from the nasal pressure signal. Flow limitation is present when peak flow occurs very early or very late in inspiration. Inspiratory flow limitations (IFLs) are usually terminated by arousals, which may contribute to acute elevations in BP through sympathetic activation.[31] They showed that a higher NREM IFL was associated with a lower diastolic BP after adjusting for baseline covariates, hypoxia, and sleep depth. REM IFL was not associated with systolic and diastolic BP after covariate adjustment. A higher NREM duty cycle was associated with a lower systolic BP after adjusting for baseline covariates; this association was significant after adjusting for HB and sleep depth. They also reported a higher REM duty cycle was associated with lower systolic BP. There were no significant associations of NREM or REM duty cycle with diastolic BP. In this study, they hypothesized that metrics of increased inspiratory resistance (IFL, duty cycle) would be associated with higher BP; however, they found the opposite. Investigating these metrics on cohorts with different characteristics (eg, age, BMI) might reveal more information about this metric.

Cognitive function– and vigilance-related outcomes

Of 10 studies that investigated cognitive function– and vigilance-related outcomes, the majority of studies reported EEG-related metrics associated with this group of outcomes.

Autonomic/hemodynamic metrics: 1 study

Finding the association between this group of metrics and cognitive outcomes reported in just one recent study.

Pulse arrival time (PAT)

PAT was introduced previously (see above). Since acute hypertension is known to be linked to an increased risk of cerebral microbleeds, Alomri and colleagues[45] investigated whether nocturnal elevations in BP derived from PAT were associated with cognitive dysfunction in patients with OSA. The maximum value of nocturnal systolic BP and the difference between resting and nocturnal systolic BP peaks were independently associated with poor performance on the Austin Maze test (a test of visuospatial dysfunction) after controlling for several confounders including age, smoking status, depressive symptoms, hypoxia, and sleep fragmentation. No association was observed with sustained attention, reaction time, or memory. Using PAT as a surrogate of BP might be able to predict cognitive dysfunction in patients with OSA; however, evaluation of this metric on different metrics with greater size is undeniable.

EEG metrics: 6 studies

Six out of 9 studies reported associations between EEG-related metrics and cognitive function and vigilance outcomes (**Table 2**).

ORP

Azarbarzin and colleagues[46] studied the relationship between interhemispheric ORP coherence (LR-OPR, correlation between ORP from left and right hemispheres) and the risk of car crashes. Patients in the highest quartile of LR-OPR had a 62% lower risk of crash compared with the lowest quartile. Although the methods for derivation of this metric are easy to understand, the mean age of participants in this study was high. Moreover, the lack of control for confounders limits the impact of this study.

EEG metrics

Djonlagic and colleagues[47] studied which aspect of sleep EEG was most strongly associated with cognitive performance and processing speed in adult patients from the MrOS and MESA cohorts. Using EEG spectrum analysis from over 150 objective sleep metrics, they found 23 metrics associated with cognitive performance. Promising metrics fell across 3 broad classes: (class 1) sleep duration and continuity (eg, REM duration [min], sleep efficiency); (class 2) spindle activity and spindle–slow oscillation coupling (eg, fast spindle count [N2], slow spindles–slow oscillation coupling, fast spindles–slow oscillation coupling; fast spindles center frequency = 15 Hz and slow spindles center frequency = 11 Hz); and (class 3) slow-wave sleep (eg, slow/delta [N3], slow/delta [N2 + N3], slow oscillations wavelength [N3]). As results, in terms of class 1 metrics, increased REM duration, sleep efficiency, and sleep maintenance efficiency were associated with better cognitive performance. In terms of class 2, higher count and integrated spindle activity were associated with better cognitive performance for both fast and slow N2 spindles, as well as higher fast spindle integrated spindle activity per minute. For class 3, higher relative slow power (during both N2 and N3) but lower relative delta power (N3) were associated with worse cognitive performance.

Spindle Burst Index

A novel metric based on bursts of spindles (Spindle Burst Index [SBI]) was reported by McCloy and colleagues.[48] They examined links between SBI and objective vigilance as assessed by the Psychomotor Vigilance Test (PVT) indices (number of lapses and reaction time) using data acquired from diagnostic PSGs. The SBI was defined as the percentage of burst spindles in a sleep block (eg, stage 2 sleep). They classified sleep spindles as bursts if they occurred within a maximum inter-spindle interval of 20 seconds (ie, spindles occurred in proximity to each other). Spindle characteristics were used to model standardized (z score) lapse and median reaction time (MdRT) scores, and to groups based on zLapse and zMdRT scores. Their proposed model using spindle characteristics mapped to MdRT with an accuracy of 91.9% (sensitivity and specificity of the model were 88.9%, and 89.1%, respectively, for detecting patients with the lowest median reaction times as a vigilance marker). More research on this model needs to be done to validate their proposed model.

EEG power

Vakulin et al[49] used EEG power spectral analysis (absolute EEG spectral power across all frequencies [0.5–32 Hz]) to identify predictors of driving simulator performance. Significant predictors of worse steering deviation were greater total EEG power during NREM and REM sleep, greater beta (15–32 Hz) EEG power in NREM, and greater delta (0.5–4.5 Hz) EEG power in REM as well as sleep-onset latency.

Arousal duration

Schwartz and Moxley[50] examined longer EEG arousal duration as a novel arousal definition and showed that longer durations (15–60 seconds) were better associated with self-reported sleepiness in patients with OSA than standard arousal durations (3–10 seconds). A study by Duce and colleagues[51] examined the extent to which changing the minimum cortical arousal duration improved the link between sleep fragmentation and neurocognitive outcomes. They showed that there was no difference between the impaired and unimpaired groups in the PVT test (The PVT outcomes were calculated: mean 1/reaction time [RT], median RT, slowest 10% 1/RT, and the number of lapses) with respect to the standard, 3-second minimum EEG arousal duration (P = .220). However, the impaired group showed significantly increased EEG arousal indices that required a minimum duration of 5 seconds (P = .034), 7 seconds (P = .041), and 15 seconds (P = .036). Moreover, comparisons of receiver-operator characteristic (ROC) curves of minimum EEG arousal duration thresholds for the identification of patients with OSA with impaired PVT performance indicated the AUC, the specificity, and the positive likelihood ratio increased as the threshold for the duration of EEG arousals increased.

Oximetric metrics: 1 study

Desaturation severity and obstructive severity

Kainulainen and colleagues[52] examined how metrics derived from oximetry signal (desaturation duration, desaturation severity, and obstruction severity [explained in the previous section]) were associated with impaired vigilance (PVT reaction time and number of lapses). They showed that the duration of apneas and hypopneas, duration of desaturations, and obstruction severity do not seem to affect PVT performance as much as the severity of desaturations.

Respiratory event–related metrics: 2 studies

Apnea or hypopnea load

Goh and colleagues[53] sought to investigate if apnea or hypopnea load, which considers event duration and not just the presence or absence of respiratory events, had a better correlation with the Epworth Sleepiness Scale score than the AHI. Using linear regression analysis, apnea load (P = .005) was independently associated with Epworth Sleepiness Scale score. Moreover, in 2007, Mediano and colleagues[54] investigated the association between apnea duration and excessive daytime sleepiness in patients with OSA. They showed that apnea duration in the group with excessive daytime sleepiness was higher than in the non–excessive daytime sleepiness group (ie, 29 ± 8 and 22 ± 7, respectively; P = .008). Both of this metrics have been examined in the association of apnea and hypopnea load in 2 different cohorts. Their results showed that apnea load could be beneficial for predicting cognitive dysfunction– and vigilance-related outcomes.

DISCUSSION

In this comprehensive systematic review, we identified 31 studies that identified promising alternative PSG metrics that have the potential to better predict OSA-related complications than standard metrics. These alternative metrics can leverage the richness of the raw PSG data into generating a more nuanced description of the disease. Broadly speaking, we found 4 general categories of alternative metrics pertaining to hemodynamic-related, EEG-related, desaturation indices, and respiratory event data. These metrics were used to predict a broad range of OSA-associated outcomes, including CVD, cognitive dysfunction, hypertension, CKD, car crash risk, and all-cause mortality. Identifying biometric profiles based on PSG may help stratify patients more at risk of the effects of OSA and could significantly affect patient management. For example, if a patient was identified as having a high risk of CVD, one would be more aggressive in terms of OSA management and management of other CV risk factors (eg, hypertension, hyperlipidemia, inactivity). In addition, these profiles may help identify potential pharmacologic targets for therapy; for example, if a patient with high sympathetic activity was identified based on PSG metrics, they might be more likely to benefit from a beta-blocker to improve CV risk.[55]

We also identified several limitations in the studies published to date. Many of the studies included were retrospective analyses of prospective outcomes and used established cohorts. Most were community-based cohorts and their generalizability to patients seen in sleep clinics could be questioned. In addition, for SHHS and MrOS specifically, the mean age was high (ie, 76.6 and 64 years for MrOS and SHHS, respectively[33]) and MrOS specifically only studied men, which might again limit generalizability. However, some of these metrics (eg, hypoxic burden[36]) have been validated in both clinical and community-based cohorts. In order to bring these and other metrics to clinical use, future work should focus not only on identifying more novel metrics but also to validate previously identified metrics across other populations. There is also an urgent need to apply them to the prospective studies, with prespecified analyses and outcomes. In addition, we would envision that these features might be used to select patients for inclusion in randomized controlled trials of OSA therapy. For example, if features indicative of patients at high risk of incident CV risk could be identified, they may be targeted for clinical trials examining impacts of therapy on CV risk reduction. Furthermore, we would envision that eventually these metrics could be incorporated into machine-learning models that could help find the best metrics or combination of metrics associated with specific outcome or refine prediction models for OSA-related complications. However, we feel that different metrics would likely be more useful for particular outcomes; for example, metrics predictive of CV risk might not be that helpful in predicting the risk of dementia.

The PSG provides a wealth of physiologic information that goes beyond the AHI and other standard PSG metrics that might help risk-stratify patients with adverse health outcomes. OSA is being increasingly considered a heterogeneous disease both from the perspective of underlying mechanisms as well as in terms of clinical manifestations. A long-term OSA management outlook where clinicians and patients are provided a more nuanced representation of their disease, especially with regard to the risk of future adverse OSA-related outcomes, is an exciting prospect for the field of sleep medicine.

ABBREVIATIONS

AB, arousal burden
AC, acceleration capacity
AHI, apnea-hypopnea index
BP, blood pressure
CKD, chronic kidney disease
CPAP, continues positive airway pressure
CPC, cardiopulmonary coupling
Ct, circulation time
CV, cardiovascular
CVD, cardiovascular disease
DC, deceleration capacity
ECG, electrocardiogram
EEG, electroencephalography
EMG, electromyography
HB, hypoxic burden
HF, high frequency
HRV, heart rate variability
IFL, inspiratory flow limitation
LF, low frequency
LFCt, lung to finger circulation time
MASE, major adverse cardiovascular event
MESA, Multi-Ethnic Study of Atherosclerosis
MrOS, Osteoporotic Fractures in Men Study
NREM, non–rapid eye movement
ODI, oxygen desaturation index
ODR, oxygen desaturation rate
ORP, odds ratio product
OSA, obstructive sleep apnea
PAT, pulse arrival time
PPG, photoplethysmography
PRV, pulse rate variability
PSG, polysomnography
PVT, Psychomotor Vigilance Test
REDTA, respiratory event desaturation transient area
REM, rapid eye movement
SBI, Spindle Burst Index
SD, standard deviation
SHHS, Sleep Heart Health Study
SOF, Study of Osteoporotic Fractures
SpO_2, oxygen saturation

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May 30, 2022
Submitted in final revised form September 9, 2022
Accepted for publication September 12, 2022

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the University of British Columbia (UBC). Dr. Najib Ayas's funding: Vancouver Coastal Health Research Institute Innovation funding, BC Lung Association Operating Grant, Canadian institutes of health research Operating Grant. Dr. Rachel Jen: VCHRI Investigator Grant. Dr. Azarbarzin reports grant funding from National Institute of Health, American Heart Association, American Academy of Sleep Medicine Foundation, and Somnifix. There are no other funding sources from other authors. A.A. serves as a consultant for Apnimed, Somnifix, Inspire, and Respicardia, outside the submitted work. A.A. is an author in some of the studies reported in this review. The other authors report no conflicts of interest.