THE COMPLEX INTERACTION BETWEEN BIOLOGICAL, METABOLIC AND NEUROLOGIC DYSREGULATION IN OBSTRUCTIVE SLEEP APNEA

EDITED BY: Georgia Trakada, Carolina Lombardi and Beat Knechtle
PUBLISHED IN: Frontiers in Psychiatry and Frontiers in Neurology

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88971-773-6
DOI 10.3389/978-2-88971-773-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

THE COMPLEX INTERACTION BETWEEN BIOLOGICAL, METABOLIC AND NEUROLOGIC DYSREGULATION IN OBSTRUCTIVE SLEEP APNEA

Topic Editors:
Georgia Trakada, National and Kapodistrian University of Athens, Greece
Carolina Lombardi, Istituto Auxologico Italiano (IRCCS), Italy
Beat Knechtle, University of Zurich, Switzerland

Citation: Trakada, G., Lombardi, C., Knechtle, B., eds. (2021). The Complex Interaction Between Biological, Metabolic and Neurologic Dysregulation in Obstructive Sleep Apnea. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88971-773-6

Table of Contents

frontiers in Psychiatry

EDITORIAL
published: 05 October 2021
doi: 10.3389/fpsyt.2021.770930

Editorial: The Complex Interaction Between Biological, Metabolic and Neurologic Dysregulation in Obstructive Sleep Apnea

Georgia Trakada[1]*, *Carolina Lombardi*[2] *and Beat Knechtle*[3]

[1] School of Health Sciences, National and Kapodistrian University of Athens, Athens, Greece, [2] Istituto Auxologico Italiano (IRCCS), Milan, Italy, [3] Institut für Hausarztmedizin, Universitätsklinikum Zürich, Zurich, Switzerland

Keywords: obstructive sleep apnea (OSA), visceral obesity, cardiometabolic risk, chronic mental disease, inflammation

Editorial on the Research Topic

The Complex Interaction Between Biological, Metabolic and Neurologic Dysregulation in Obstructive Sleep Apnea

OPEN ACCESS

Edited by:
David Gozal,
University of Missouri, United States

Reviewed by:
Clementine Puech,
University of Missouri, United States

***Correspondence:**
Georgia Trakada
gtrakada@hotmail.com

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *05 September 2021*
Accepted: *15 September 2021*
Published: *05 October 2021*

Citation:
Trakada G, Lombardi C and Knechtle B (2021) Editorial: The Complex Interaction Between Biological, Metabolic and Neurologic Dysregulation in Obstructive Sleep Apnea. Front. Psychiatry 12:770930. doi: 10.3389/fpsyt.2021.770930

Obstructive sleep apnea (OSA) is a prevalent chronic disorder characterized by repetitive apneas and hypopneas during sleep, leading to intermittent hypoxia (IH) and recurrent arousals from sleep, leading to sleep fragmentation and reduced sleep efficiency (1). Accumulated evidence suggests that OSA—and the underlying biological, metabolic, and neurologic dysregulation—is closely associated with cardiometabolic disorders, neurocognitive dysfunction, and chronic mental diseases (2–4) (**Figure 1**). In this Research Topic we aimed to further evaluate symptoms and specific characteristics of OSA patients and their possible interactions in the progression to different disease states in each individual.

In a nationwide, stratified, epidemiological survey in Cyprus ($n = 4{,}118$), Frangopoulos et al. demonstrated that 155/264 randomly selected adults that underwent a type III sleep study, had an Apnea/Hypopnea Index (AHI) ≥ 5. These newly diagnosed OSA patients were categorized as symptomatic or asymptomatic, according to the Epworth Sleepiness Scale (ESS) and/or the Athens Insomnia Scale (AIS). The two groups did not differ in terms of OSA severity and in cardiometabolic comorbidities; however, symptomatic patients expressed more often both depression and anxiety when compared to asymptomatic patients, because of a poorer subjective sleep quality.

In another cross-sectional study of working adults in Kuwait ($n = 651$), Al-Qattan et al. estimated that 20% of participants were at high risk for OSA, according to the Berlin Questionnaire. The risk factors associated with elevated OSA probability were older age, obesity, lower educational level, current smoking status, no physical activity, increased television viewing, increased working hours, and short sleep duration. Individuals at high risk for OSA suffered more often than those at low risk from arterial hypertension, diabetes mellitus, insomnia, and depression.

Mohammadi et al. revealed that moderate/severe OSA was associated with a significantly lower spindle density in N3 and a shorter spindle duration in N2, whereas mild OSA showed no significant adverse effect on sleep spindle characteristics. Sleep spindles are associated with cognitive, emotional, and social processes and lower sleep spindle activity can be responsible for the deterioration of memory and cognition in OSA.

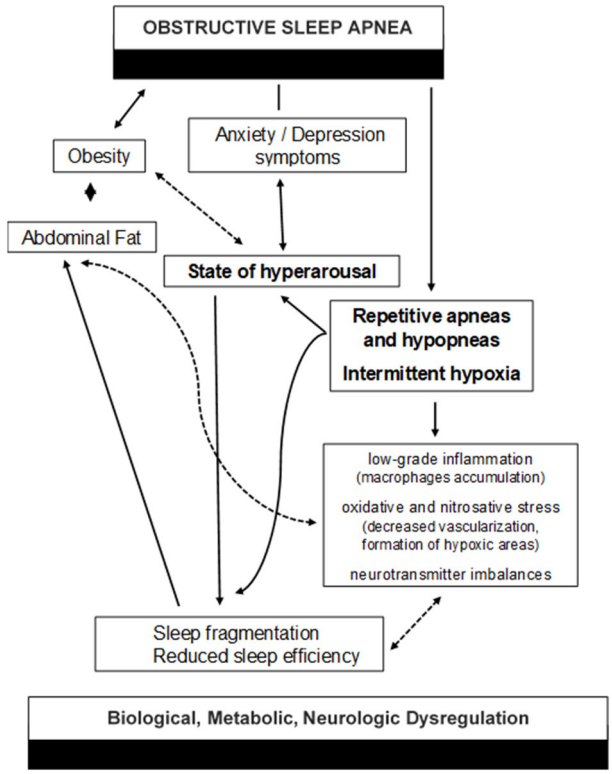

FIGURE 1 | The vicious cycle between biological, metabolic, and neurologic dysregulation in OSA.

Feng et al. evaluated the associations between objective sleep parameters derived via polysomnography (PSG) and metabolic indices. Although the observed associations were weak, both sleep structure and sleep duration affected the metabolic status of the participants. Specifically, the microarousal index (MAI)—an indicator of sleep fragmentation—significantly correlated with glucose levels and lipids metabolism, independently of respiratory indices during sleep.

Finally, Qin et al. reviewed the data about heart rate variability (HRV), as a reliable and non-invasive measure of neuro-cardiac autonomic regulatory mechanisms in different aspects of OSA. Altered HRV features can be good predictors of cardiovascular morbidity and mortality in OSA.

The major challenge in studying OSA is that the disease is heterogeneous and multifactorial. The clinical OSA phenotypes can vary in symptoms; sleepy vs. insomniac vs. asymptomatic patient. Also, the underlying pathophysiological phenotypes of OSA can be anatomical or non-anatomical, like functional impairment of pharyngeal dilator muscles during sleep, low respiratory arousal threshold and increased propensity for awakenings, or respiratory control instability because of the high loop gain mechanism. However, behind OSA and apnea-related parameters (AHI, average saturation of hemoglobin with oxygen as measured by pulse oximetry [SpO_2], and percentage of sleep time with $SpO_2 < 90\%$, $t < 90$), there is always a common denominator, the sleep process, that affects clinical picture and comorbidity. In all valuable contributions in this Research Topic, subjective or objective disturbed sleep was mainly associated with symptoms of anxiety and depression, neurocognitive defects, and cardiometabolic dysregulation.

The vicious cycle between biological, metabolic, and neurologic dysregulation in OSA still not clear and more studies are needed to be conducted to better ascertain these relationships. Future studies should extensively focus on sleep, in terms of quality, duration, circadian rhythms and architecture—both in OSA patients and in general population—to better clarify these complicated underlying pathophysiological mechanisms.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic and Coding Manual. 3rd ed.* Westchester, NY: American Academy of Sleep Medicine (2014).
2. Kallianos A, Trakada G, Papaioannou T, Nikolopouloss I, Mitrakou A, Manios E, et al. Glucose and arterial blood pressure variability in obstructive sleep apnea syndrome. *Eur Rev Med Pharmacol Sci.* (2013) 17:1932–7.
3. Trakada G, Chrousos G, Pejovic S, Vgontzas A. Sleep apnea and its association with the stress system, inflammation, insulin resistance and visceral obesity. *Sleep Med Clin.* (2007) 2:251–61. doi: 10.1016/j.jsmc.2007.04.003
4. Knechtle B, Economou NT, Nikolaidis PT, Velentza L, Kallianos A, Steiropoulos P, et al. Clinical characteristics of obstructive sleep apnea in psychiatric disease. *J Clin Med.* (2019) 8:534. doi: 10.3390/jcm8040534

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 February 2021
doi: 10.3389/fneur.2021.606031

The Associations Between Sleep Architecture and Metabolic Parameters in Patients With Obstructive Sleep Apnea: A Hospital-Based Cohort Study

Nana Feng[1], *Jundong Yang*[2], *Huajun Xu*[3,4,5], *Chujun Zhang*[3,4,5], *Fan Wang*[3,4,5], *Xiaolin Wu*[6]* *and Meizhen Gu*[7]*

[1] Department of Respiratory and Critical Medicine, Shanghai Eighth People's Hospital Affiliated to Jiangsu University, Shanghai, China, [2] Department of Medicine, Jiangsu University, Zhenjiang, China, [3] Department of Otolaryngology Head and Neck Surgery and Center of Sleep Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China, [4] Otolaryngological Institute of Shanghai Jiao Tong University, Shanghai, China, [5] Shanghai Key Laboratory of Sleep Disordered Breathing, Shanghai, China, [6] Central Laboratory of Shanghai Eighth People's Hospital Affiliated to Jiangsu University, Shanghai, China, [7] Department of Otolaryngology-Head & Neck Surgery, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai, China

OPEN ACCESS

Edited by:
Ahmed S. BaHammam, King Saud University, Saudi Arabia

Reviewed by:
Oreste Marrone, National Research Council (CNR), Italy
Lourdes DelRosso, University of Washington, United States

***Correspondence:**
Xiaolin Wu
wuxiaolin999@hotmail.com
Meizhen Gu
gmzabc@163.com

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Neurology

Received: *15 September 2020*
Accepted: *07 January 2021*
Published: *10 February 2021*

Citation:
Feng N, Yang J, Xu H, Zhang C, Wang F, Wu X and Gu M (2021) The Associations Between Sleep Architecture and Metabolic Parameters in Patients With Obstructive Sleep Apnea: A Hospital-Based Cohort Study. Front. Neurol. 12:606031. doi: 10.3389/fneur.2021.606031

Background and Objectives: The associations between objective sleep architecture and metabolic parameters have been rarely studied in patients with obstructive sleep apnea (OSA). Here, we evaluated the associations between objective sleep measures derived *via* polysomnography (PSG) and metabolic parameters.

Methods: A total of 2,308 subjects with suspected OSA were included. We measured common metabolic parameters such as body mass index (BMI) and glucose, insulin, blood pressure, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels. All subjects underwent full-night PSG. PSG sleep parameters included total sleep time (TST), time spent in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, sleep efficiency, and the microarousal index (MAI).

Results: The TST correlated with the BMI, glucose level, and systolic blood pressure. The SWS/TST ratio correlated with BMI and glucose, TC, and TG levels. The REM/TST ratio correlated with BMI, glucose, insulin, and TG levels, and diastolic blood pressure. We found significant relationships between sleep efficiency and BMI, glucose levels, and TG levels. The MAI was significantly correlated with all metabolic parameters. After adjustment for age, gender, smoking status, alcohol use, apnea hypopnea index, and oxygen desaturation index (ODI), multiple linear regression analysis showed that the MAI was independently associated with glucose level, TC, HDL, and LDL. REM/TST ratio was positively associated with diastolic blood pressure but negatively associated with glucose metabolism.

Conclusions: Though some independent correlation between sleep and metabolic parameters was confirmed, only weak associations were observed, suggesting a clinically negligible influence of sleep structure. Further prospective studies are warranted to confirm our findings.

Keywords: obstructive sleep apnea, metabolism, sleep architecture, polysomnography, sleep apnea

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of death worldwide. CVD prevalence is rising with increasing tobacco and alcohol use, physical inactivity, and consumption of high-fat/sugar diets (1). Obstructive sleep apnea (OSA) is a risk factor for CVD (2). OSA is commonly associated with common cardiovascular risk factors such as certain components of metabolic syndrome (MS) including dyslipidemia, insulin resistance, hypertension, diabetes, and obesity (3–6). Both subjective and objective sleep disturbances increase CVD risk. Between 6 and 8 h of sleep per day reduces the risk of major cardiovascular events (7). Weak associations have been reported among excessive daytime sleepiness, CVD, and coronary heart disease risk (8). The apnea–hypopnea index (AHI) and oxygen desaturation index (ODI), derived *via* polysomnography (PSG), were independently associated with cardiovascular risk factors including mean oxygen saturation (9). However, the contributions of other OSA-related sleep characteristics (quantitative measures of sleep disturbance) to common CVD risk (i.e., metabolic parameters) have not been well-studied. In particular, few studies have explored the relationships of total sleep time (TST), time spent in slow-wave sleep (SWS) and rapid eye movement (REM) sleep, sleep efficiency, and the microarousal index (MAI) with metabolic parameters. Thus, this study tested for independent associations between these sleep parameters (based on PSG) and the metabolic risk factors of obesity, high glucose and insulin levels, and a disturbed lipid profile in patients with OSA. We hypothesized that subjects with poor sleep characteristics were more likely to have detrimental metabolic statuses.

METHODS

Population Sampling

This observational study consecutively enrolled adults who visited the sleep center of Shanghai Jiao Tong University Affiliated Sixth People's Hospital from January 2010 to December 2015. The study was approved by the Ethics Committee of our hospital [2019-KY-050(K)]. Informed consent was obtained from all participants, who completed questionnaires on medical history, smoking status, alcohol use, and subjective sleep quality. The subjects were classified as smokers (ex- or current) or never-smokers and as current alcohol drinkers or nondrinkers. The exclusion criteria were as follows: (1) aged <18 years; (2) previous upper airway surgery, use of an oral appliance, or continuous positive airway pressure treatment; (3) severe chronic systemic disease (i.e., hepatic, pulmonary, and cardiac failure); (4) another sleep disorder (severe insomnia, restless leg syndrome, or narcolepsy) or a mental condition; (5) current use of antipsychotics; (6) use of medications to treat hypertension, diabetes mellitus, or hyperlipidemia; and (7) missing data. Ultimately, 2,308 participants were included in the analysis.

Metabolic Parameters

Height and weight were measured as described previously (10). Blood pressure was measured twice using the left arm after a 15-min rest period in the evening at the time of the study and blood pressure was taken at the same time (8:00 pm) for all participants, and the mean value was calculated. Fasting venous blood was collected from each participant at 07:00 for all participants. Fasting venous blood was collected for analyses of insulin and glucose levels and the lipid profile [total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] in the laboratory of our hospital by the same procedures, i.e., serum lipid and fasting serum glucose levels were measured in the hospital laboratory using an autoanalyzer (H-7600; Hitachi, Tokyo, Japan). The body mass index (BMI) was calculated using height and weight data. MS was defined as suggested by the Adult Treatment Panel Report III based on the presence of at least three of the following: (1) abdominal obesity [waist circumference (WC) >102 and 88 cm in males and females, respectively]; (2) elevated TG level [≥1.7 mmol/L (>150 mg/dl)]; (3) low HDL-C level [<1.03 mmol/L (40 mg/dl) and <1.20 mmol/L (50 mg/dl) in males and females, respectively]; (4) elevated blood pressure (≥130/≥85 mmHg) or a history of hypertension; and (5) an elevated fasting blood glucose level (≥5.6 mmol/L) or any history of type 2 diabetes mellitus (11).

Polysomnography

All participants underwent full-night PSG (Alice 4 or Alice 5; Respironics, Pittsburgh, PA, USA). The data were recorded using 18 channels: six for electroencephalography (EEG), two for electrooculography (EOG), two for surface (chin) electromyography (EMG), three for electrocardiography (ECG), and one each for oronasal temperature, nasal pressure, thoracic and abdominal belt, body position, and oxygen saturation. Polysomnographic variables were scored manually by skilled

Abbreviations: OSA, obstructive sleep apnea; PSG, polysomnography; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; MAI, microarousal index; TST, total sleep time; SWS, slow-wave sleep; REM, rapid eye movement; CVD, cardiovascular disease.

technicians according to the 2012 guidelines of the American Academy of Sleep Medicine (AASM) (12); if the PSG were recorded before 2012, they were reanalyzed according to the same 2012 AASM criteria. Apnea was defined as at least 90% reduction in airflow for at least 10 s; hypopnea was defined as at least 50% reduction in airflow for at least 10 s or longer and accompanied by at least 3% reduction in oxygen saturation or arousal, as described previously (5). The AHI was given by the average number of apneas/hypopneas per hour of sleep. The ODI was given by the number of times that oxygen saturation fell by more than 3% per hour of sleep. The MAI was given by the mean number of arousals per hour of sleep. The TST was recorded as the total number of minutes of any form of sleep, from onset to morning awakening. Sleep efficiency was given by the ratio of TST to the time spent in bed. SWS (stage N3) and REM sleep durations were also recorded.

Statistical Analysis

All statistical tests were performed using SPSS software (ver. 22.0; IBM SPSS Statistics, IBM Corp., Armonk, NY, USA), and a two-sided p-value <0.05 was considered significant. The raw data were subjected to Kolmogorov–Smirnov testing. Non-normally distributed data were normalized *via* log transformation. Continuous variables are shown as mean ± standard deviation and categorical variables as percentages. Student's t-test or one-way analysis of variance (ANOVA) was used to test for differences between the groups in univariate variables. Spearman correlation analysis was used as appropriate to examine bivariate associations between sleep architecture and metabolic variables. Multiple linear regression models were used to identify independent relationships between sleep parameters and metabolic variables after controlling for age, sex, smoking status, and alcohol consumption or with additional AHI and ODI.

RESULTS

Baseline Characteristics

A total of 2,308 subjects who were primary snorers were included in the final analysis. Their baseline anthropometric, metabolic, and polysomnographic data are listed in **Table 1**. We assigned the participants to two groups according to the AHI; one group had none-to-mild OSA (AHI <15/h) ($n = 1{,}021$) and the other had moderate-to-severe OSA (AHI ≥15/h) ($n = 1{,}287$). Compared to those with none-to-mild OSA, subjects with moderate-to-severe OSA were older (41.20 vs. 38.84 years, $p < 0.001$) and had higher BMI (27.05 vs. 24.10 kg/m^2, $p < 0.001$), systolic blood pressure (SBP) (125.66 vs. 120.41 mmHg, $p < 0.001$), and diastolic blood pressure (DBP) (80.88 vs. 77.12, $p < 0.001$) values, as well as higher glucose (5.45 vs. 5.05 mmol/L, $p < 0.001$), insulin (13.33 vs. 9.01 μU/mL, $p < 0.001$), TC (4.86 vs. 4.50 mmol/L, $p < 0.001$), TG (2.11 vs. 1.42 mmol/L, $p < 0.001$), and LDL (3.08 vs. 2.78 mmol/L, $p < 0.001$) levels. In terms of objective sleep parameters, patients with moderate-to-severe OSA spent less time in SWS (11.49 vs. 14.92%, $p < 0.001$) and REM sleep (8.88 vs. 10.38%, $p < 0.001$) and had higher sleep efficiency (0.82 vs. 0.78, $p < 0.001$) and MAI values (31.38 vs. 17.65/h, $p < 0.001$).

Relationships Between Sleep Parameters and Metabolic Parameters

The TST correlated with BMI, glucose level, and SBP. The SWS/TST ratio correlated with BMI and glucose, TC, and TG levels. The REM/TST ratio correlated with BMI glucose, insulin and TG levels, and DBP. Sleep efficiency was significantly associated with BMI and glucose and TG levels. The MAI correlated significantly with all metabolic parameters (**Table 2**).

To minimize the effect of OSA, we excluded subjects with a high AHI (≥15/h). Sensitivity analysis revealed significant correlations between the TST and HDL and LDL levels; between the SWS/TST ratio and glucose level; between the REM/TST ratio and insulin and TG levels, SBP, and DBP; between sleep efficiency and the HDL level; and between the MAI and TC and LDL levels (**Table 3**).

We performed multiple linear regression analyses to identify independent relationships between sleep parameters and metabolic variables after adjusting for multiple confounding factors, including age, sex, smoking status, and alcohol use (model 1). The TST, SWS/TST ratio, and MAI were independent predictors of BMI. Also, sleep efficiency and the MAI were independent predictors of glucose level. The MAI was an independent predictor of insulin level, blood pressure, and the lipid profile (**Table 4**). REM/TST ratio was negatively associated with BMI, glucose level, insulin level, and TG level. The results were stable when we excluded subjects with a high AHI (≥15/h) (**Table 5**). After adjusting for variables in model 1 and additional AHI and ODI (model 2), sleep efficiency and the MAI were independent predictors of glucose level. The MAI was an independent predictor of TC, HDL, and LDL level. The REM/TST ratio was negatively associated with BMI, glucose level, and TG level (**Table 4**). Similarly, the results were also stable when we excluded moderate to severe OSA (**Table 5**).

As we can see, even when excluding patients with AHI ≥15 from the multivariate analysis, though some independent correlation between sleep and metabolic parameters was confirmed, only weak associations were observed, suggesting a clinically negligible influence of sleep structure.

DISCUSSION

To the best of our knowledge, few studies have explored the association between sleep architecture and metabolic status. We enrolled a relatively large number of subjects and found that many metabolic variables were affected by sleep parameters. A higher proportion of REM sleep was an independent risk factor for elevated blood pressure, and a higher MAI was an independent risk factor for suboptimal lipid metabolism. After controlling for OSA, these findings remained significant. However, though some independent correlation between sleep and metabolic parameters was confirmed, only weak associations were observed, suggesting a clinically negligible influence of sleep structure.

OSA is commonly accompanied by disturbed sleep architecture, including a reduced proportion of SWS sleep

TABLE 1 | Basic characteristics of all participants.

Characteristic	All (n = 2,308)	AHI <15/h(n = 1,021)	AHI ≥15/h (n = 1,287)	p-value
Demographics				
Age, years	40.16 ± 11.18	38.84 ± 11.58	41.20 ± 10.74	<0.001
Male (%)	79.5	66.8	89.7	<0.001
BMI, kg/m^2	25.74 ± 3.77	24.10 ± 3.31	27.05 ± 3.61	<0.001
Smokers, *n* (%)	773 (33.5)	237 (23.2)	536 (41.6)	<0.001
Alcohol consumption, *n* (%)	1,028 (44.5)	373 (36.5)	655 (50.9)	<0.001
Biochemical variables				
Glucose (mmol/L)	5.27 ± 0.99	5.05 ± 0.81	5.45 ± 1.08	<0.001
Insulin (μU/mL)	11.41 ± 7.95	9.01 ± 5.61	13.33 ± 8.96	<0.001
SBP, mmHg	123.33 ± 14.69	120.41 ± 13.60	125.66 ± 15.11	<0.001
DBP, mmHg	79.22 ± 10.94	77.12 ± 10.02	80.88 ± 11.34	<0.001
TC (mmol/L)	4.70 ± 0.97	4.50 ± 0.99	4.86 ± 0.93	<0.001
TG (mmol/L)	1.80 ± 1.48	1.42 ± 1.02	2.11 ± 1.71	<0.001
HDL (mmol/L)	1.13 ± 2.57	1.14 ± 0.27	1.13 ± 3.43	0.915
LDL (mmol/L)	2.94 ± 0.8	2.78 ± 0.80	3.08 ± 0.78	<0.001
Polysomnography				
Total sleep time, min	373.65 ± 73.08	363.50 ± 76.54	381.63 ± 69.18	<0.001
SWS, % of TST	13.0 ± 10.7	14.92 ± 10.67	11.49 ± 10.47	<0.001
REM, % of TST	9.54 ± 6.86	10.38 ± 7.11	8.88 ± 6.59	<0.001
Sleep efficiency, %	0.80 ± 0.16	0.78 ± 0.17	0.82 ± 0.16	<0.001
MAI	25.34 ± 19.67	17.65 ± 14.09	31.38 ± 21.26	<0.001
AHI	28.54 ± 26.72	4.94 ± 4.32	47.22 ± 21.78	<0.001
ODI	29.36 ± 28.20	7.16 ± 13.21	46.94 ± 24.25	<0.001

Data are presented as numbers (percentages) or mean ± SD.
Differences in baseline characteristics between patients with AHI <15/h and AHI ≥15/h were explored using the independent t-test or chi-square test.
AHI, apnea–hypopnea index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SWS, slow-wave sleep; TST, total sleep time; REM, rapid eye movement; ODI, oxygen desaturation index; MAI, microarousal index.

TABLE 2 | Bivariate correlations between sleep parameters and metabolic variables in all subjects.

	BMI (kg/m^2)	Glucose (mmol/L)	Insulin (μU/mL)	SBP (mmHg)	DBP (mmHg)	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
Total sleep time, min	0.093**	0.075**	0.022	0.042*	0.040	0.003	0.031	0.006	−0.016
SWS, % of TST	−0.119**	−0.086**	−0.005	−0.034	−0.011	−0.058**	−0.056**	0.027	−0.029
REM, % of TST	−0.099**	−0.075**	−0.053*	0.034	0.058**	−0.036	−0.064**	0.014	0.008
Sleep efficiency, %	0.105**	0.089**	0.003	0.006	0.002	0.018	0.042*	−0.005	0.020
MAI	0.230**	0.145**	0.225**	0.090**	0.137**	0.134**	0.145**	0.050*	0.182**

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SWS, slow-wave sleep; TST, total sleep time; REM, rapid eye movement; MAI, microarousal index.
All numbers represent correlation coefficients.
*Spearman correlation analysis: **significant at the 0.01 level; *significant at the 0.05 level.*

and lower sleep efficiency in children with a common phenotype of OSA (13). In adults with OSA, regardless of sleep duration, alterations in sleep architecture prevent adequate rest (14). We also found shorter SWS and REM sleep durations and a higher MAI in OSA patients. A previous study found that more SWS, increased sleep efficiency, and a greater TST improved glucose and insulin homeostasis in overweight/obese children and adolescents (15). In such adolescents, insufficient/excessive sleep was associated with hyperglycemia, and a decreased SWS was linked to a decrease in insulin level (16). However, it remains unclear how sleep architecture affects the metabolic status of adults.

During REM sleep, autonomic status is unstable, reflected in fluctuations in the parasympathetic and sympathetic nervous systems. As cortical desynchronization develops during REM sleep, the respiratory and circulatory systems become increasingly unstable (17), which will affect the blood pressure. We found that a longer REM sleep duration was an independent risk factor for higher blood pressure. Persistently high levels of sympathetic activity during REM sleep may explain the increases

TABLE 3 | Bivariate correlations between sleep parameters and metabolic variables in subjects without moderate-to-severe OSA.

	BMI (kg/m^2)	Glucose (mmol/L)	Insulin (μU/ml)	SBP (mmHg)	DBP (mmHg)	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
Total sleep time, min	0.029	0.046	0.036	0.006	0.001	−0.048	0.019	−0.096**	−0.074*
SWS, % of TST	−0.048	−0.069*	0.052	−0.007	0.024	−0.016	−0.032	0.014	0.023
REM, % of TST	−0.034	−0.040	−0.082**	0.068*	0.071*	−0.006	−0.067*	0.021	0.012
Sleep efficiency, %	0.026	0.045	0.006	−0.012	−0.032	−0.037	0.015	−0.065*	−0.050
MAI	0.041	0.010	0.051	−0.020	−0.017	0.078*	0.032	0.029	0.134**

OSA, obstructive sleep apnea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SWS, slow-wave sleep; TST, total sleep time; REM, rapid eye movement; MAI, microarousal index.
***significant at the 0.01 level.*
**significant at the 0.05 level.*

TABLE 4 | Multiple linear regression analysis of the effects of sleep parameters on metabolic variables in the overall population.

	Model 1				Model 2			
Outcome	**Predictor**	***β***	**Standard error**	***p*-value**	**Predictor**	***β***	**Standard error**	***p*-value**
BMI (kg/m^2)	MAI	0.037	0.004	<0.001	REM/TST (%)	−0.025	0.011	0.016
	SWS/TST (%)	−0.030	0.007	<0.001				
	TST	0.004	0.001	<0.001				
	REM/TST (%)	−0.042	0.011	<0.001				
Glucose (mmol/L)	MAI	0.007	0.001	<0.001	MAI	0.002	0.001	0.036
	SE (%)	0.406	0.125	0.001	SE (%)	0.323	0.125	0.01
	REM/TST (%)	−0.007	0.003	0.017	REM/TST (%)	−0.006	0.003	0.048
Insulin (μU/mL)	MAI	0.086	0.008	<0.001	(-)	(-)	(-)	(-)
	REM/TST (%)	−0.076	0.023	0.001				
SBP (mmHg)	MAI	0.051	0.016	<0.001	(-)	(-)	(-)	(-)
DBP (mmHg)	MAI	0.062	0.012	<0.001	REM/TST (%)	0.132	0.033	<0.001
	REM/TST (%)	0.103	0.033	0.002				
TC (mmol/L)	MAI	0.006	0.001	<0.001	MAI	0.003	0.001	0.004
TG (mmol/L)	MAI	0.009	0.002	<0.001	REM/TST (%)	−0.009	0.004	0.043
	REM/TST (%)	−0.012	0.004	0.006				
HDL (mmol/L)	MAI	0.008	0.003	0.005	MAI	0.011	0.003	<0.001
LDL (mmol/L)	MAI	0.007	0.001	<0.001	MAI	0.005	0.001	<0.001

Model 1 was adjusted for age, sex, smoking status, and alcohol use; model 2 was adjusted for variables in model 1 and additional AHI and ODI.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SE, sleep efficiency; TST, total sleep time; REM, rapid eye movement; MAI, microarousal index.

in blood pressure. Previous studies showed that AHI during REM sleep was independently associated with hypertension, insulin resistance, MS, and diabetes (18–21). The increased numbers of apneas and hypopneas during REM sleep may also explain why blood pressure increases. However, we found that longer REM sleep proportion was associated with lower insulin and glucose (**Tables 4**, **5**). Few studies had explored the relationship between REM sleep proportion and glucose metabolism; further prospective or randomized controlled studies are warranted to confirm our findings.

Increased microarousal rate, one of the most important features of OSA, was shown to be independently associated with hyper-LDL cholesterolemia (22). We also found that the MAI was independently associated with lipid metabolism. There are several possible explanations for this: first, the MAI closely reflects sympathetic hyperactivity, which is associated with lipolysis. Second, microarousals may activate the hypothalamic–pituitary–adrenal (HPA) axis, further elevating the levels of cortisol and other hormones and thus triggering lipolysis (23). Third, microarousals are associated with systemic inflammation, which also plays an important role in lipid metabolism (24).

We found that SWS sleep duration was independently associated with insulin level, similar to a previous study reporting that decreased SWS was associated with a dose-dependent increase in OSA-associated hypertension (25). SWS is "restorative" sleep; during SWS, the sympathetic tone is weakened, slow-wave activity is increased, and cortisol secretion is decreased. Sympathetic overactivity caused by a shorter SWS stimulates insulin secretion. Thus, improvements in sleep architecture improve metabolic status.

TABLE 5 | Multiple linear regression analysis of the effects of sleep parameters on metabolic variables in subjects without OSA.

	Model 1				Model 2			
Outcome	**Predictor**	***β***	**Standard error**	***p*-value**	**Predictor**	***β***	**Standard error**	***p*-value**
BMI (kg/m^2)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Glucose (mmol/L)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Insulin (μU/mL)	REM/TST (%)	−0.074	0.025	0.003	REM/TST (%)	−0.071	0.025	0.005
	SWS/TST (%)	0.035	0.017	0.038	SWS/TST (%)	0.035	0.017	0.038
SBP (mmHg)	REM/TST (%)	0.156	0.059	0.008	REM/TST (%)	0.164	0.059	0.005
DBP (mmHg)	REM/TST (%)	0.109	0.044	0.014	REM/TST (%)	0.110	0.044	0.013
TC (mmol/L)	MAI	0.005	0.002	0.012	MAI	0.005	0.002	0.036
TG (mmol/L)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
HDL (mmol/L)	TST	0.01	0.01	<0.001	TST	0.000	0.000	0.001
LDL (mmol/L)	MAI	0.007	0.002	<0.001	MAI	0.006	0.002	0.001

Model 1 was adjusted for age, sex, smoking status, and alcohol use; model 2 was adjusted for variables in model 1 and additional AHI and ODI.
OSA, obstructive sleep apnea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TST, total sleep time; REM, rapid eye movement; MAI, microarousal index.

The strengths of our study included the relatively large sample size, adequate adjustment for potential confounders, and use of standard PSG to obtain objective measures of sleep architecture. However, several potential limitations should also be addressed. First, the cross-sectional design did not allow us to infer causality. Second, we performed PSG only once, in a laboratory environment, so there may have been a "first night effect" and the sleep architecture might have differed somewhat from normal. Third, although we enrolled residents of southeast China with similar lifestyles, we did not adjust for various factors that affect metabolic variables, including dietary components and physical activity level. Finally, this was a hospital-based study, so the findings cannot be generalized to the general population. In conclusion, whether high-quality sleep of adequate duration is required to maintain metabolic status and might reduce the risk of CVD in OSA is still uncertain. Further prospective studies are warranted to confirm our findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The authors take responsibility and vouch for the accuracy and completeness of the data and analyses. XW and MG had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. HX, XW, and MG: study design. NF, JY, HX, FW, and CZ: data collection. HX, CZ, and XW: statistical analysis. HX, NF, XW, and MG: manuscript draft. All authors have seen and approved the manuscript.

FUNDING

This study was supported by grants-in-aid from the Shanghai Municipal Commission of Science and Technology (Grant No. 18DZ2260200) and the National Natural Science Foundation of China (81900007, 81670129, 82071029).

ACKNOWLEDGMENTS

The authors acknowledge the help of all staff in establishing this sleep cohort study.

REFERENCES

1. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. *Circulation.* (2008) 117:3031–8. doi: 10.1161/CIRCULATIONAHA.107.738732
2. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol.* (2017) 69:841–58. doi: 10.1016/j.jacc.2016.11.069
3. Wang F, Xiong X, Xu H, Huang H, Shi Y, Li X, et al. The association between obstructive sleep apnea syndrome and metabolic syndrome: a confirmatory factor analysis. *Sleep Breath.* (2019) 23:1011–9. doi: 10.1007/s11325-019-01804-8
4. Xu H, Xia Y, Li X, Qian Y, Zou J, Fang F, et al. Association between obstructive sleep apnea and lipid metabolism during REM and NREM sleep. *J Clin Sleep Med.* (2020) 16:475–82. doi: 10.5664/jcsm.8242
5. Xu H, Liang C, Zou J, Yi H, Guan J, Gu M, et al. Interaction between obstructive sleep apnea and short sleep duration on insulin resistance: a

large-scale study: OSA, short sleep duration and insulin resistance. *Respir Res.* (2020) 21:151. doi: 10.1186/s12931-020-01416-x
6. Li X, Huang H, Xu H, Shi Y, Qian Y, Zou J, et al. Excessive daytime sleepiness, metabolic syndrome, and obstructive sleep apnea: two independent large cross-sectional studies and one interventional study. *Respir Res.* (2019) 20:276. doi: 10.1186/s12931-019-1248-y
7. Wang C, Bangdiwala SI, Rangarajan S, Lear SA, AlHabib KF, Mohan V, et al. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. *Eur Heart J.* (2019) 40:1620–9. doi: 10.1093/eurheartj/ehy695
8. Ogilvie RP, Lakshminarayan K, Iber C, Patel SR, Lutsey PL. Joint effects of OSA and self-reported sleepiness on incident CHD and stroke. *Sleep Med.* (2018) 44:32–7. doi: 10.1016/j.sleep.2018.01.004
9. Hausler N, Marques-Vidal P, Heinzer R, Haba-Rubio J. How are sleep characteristics related to cardiovascular health? results from the population-based hypnolaus study. *J Am Heart Assoc.* (2019) 8:e011372. doi: 10.1161/JAHA.118.011372
10. Xu H, Guan J, Yi H, Zou J, Meng L, Tang X, et al. Shanghai Sleep Health Study Research G. Elevated low-density lipoprotein cholesterol is independently associated with obstructive sleep apnea: evidence from a large-scale cross-sectional study. *Sleep Breath.* (2016) 20:627–34. doi: 10.1007/s11325-015-1262-3
11. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* (2005) 112:2735–52. doi: 10.1161/CIRCULATIONAHA.105.169404
12. Ho V, Crainiceanu CM, Punjabi NM, Redline S, Gottlieb DJ. Calibration model for apnea-hypopnea indices: impact of alternative criteria for hypopneas. *Sleep.* (2015) 38:1887–92. doi: 10.5665/sleep.5234
13. Durdik P, Sujanska A, Suroviakova S, Evangelisti M, Banovcin P, Villa MP. Sleep architecture in children with common phenotype of obstructive sleep apnea. *J Clin Sleep Med.* (2018) 14:9–14. doi: 10.5664/jcsm.6868
14. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med.* (2009) 5:519–24. doi: 10.5664/jcsm.27651
15. Zhu Y, Li AM, Au CT, Kong AP, Zhang J, Wong CK, et al. Association between sleep architecture and glucose tolerance in children and adolescents. *J Diabetes.* (2015) 7:10–5. doi: 10.1111/1753-0407.12138
16. Koren D, Levitt Katz LE, Brar PC, Gallagher PR, Berkowitz RI, Brooks LJ. Sleep architecture and glucose and insulin homeostasis in obese adolescents. *Diabetes Care.* (2011) 34:2442–7. doi: 10.2337/dc11-1093
17. Ghadami MR. Obstructive sleep apnea and hypertension: the role of altered sleep architecture. *Sleep Med.* (2018) 51:124. doi: 10.1016/j.sleep.2018.06.019
18. Aurora RN, Crainiceanu C, Gottlieb DJ, Kim JS, Punjabi NM. Obstructive sleep apnea during REM sleep and cardiovascular disease. *Am J Respir Crit Care Med.* (2018) 197:653–60. doi: 10.1164/rccm.201706-1112OC
19. Appleton SL, Vakulin A, Martin SA, Lang CJ, Wittert GA, Taylor AW, et al. Hypertension is associated with undiagnosed OSA during rapid eye movement sleep. *Chest.* (2016) 150:495–505. doi: 10.1016/j.chest.2016.03.010
20. Chami HA, Gottlieb DJ, Redline S, Punjabi NM. Association between glucose metabolism and sleep-disordered breathing during REM sleep. *Am J Respir Crit Care Med.* (2015) 192:1118–26. doi: 10.1164/rccm.201501-0046OC
21. Acosta-Castro P, Hirotsu C, Marti-Soler H, Marques-Vidal P, Tobback N, Andries D, et al. REM-associated sleep apnoea: prevalence and clinical significance in the HypnoLaus cohort. *Eur Respir J.* (2018) 52:1702484. doi: 10.1183/13993003.02484-2017
22. Qian Y, Yi H, Zou J, Meng L, Tang X, Zhu H, et al. Independent association between sleep fragmentation and dyslipidemia in patients with obstructive sleep apnea. *Sci Rep.* (2016) 6:26089. doi: 10.1038/srep26089
23. Spath-Schwalbe E, Gofferje M, Kern W, Born J, Fehm HL. Sleep disruption alters nocturnal ACTH and cortisol secretory patterns. *Biol Psychiatry.* (1991) 29:575–84. doi: 10.1016/0006-3223(91)90093-2
24. Trammell RA, Verhulst S, Toth LA. Effects of sleep fragmentation on sleep and markers of inflammation in mice. *Comp Med.* (2014) 64:13–24.
25. Ren R, Covassin N, Zhang Y, Lei F, Yang L, Zhou J, et al. Interaction between slow wave sleep and obstructive sleep apnea in prevalent hypertension. *Hypertension.* (2020) 75:516–23. doi: 10.1161/HYPERTENSIONAHA.119.13720

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 25 February 2021
doi: 10.3389/fpsyt.2021.630162

The Complex Interaction Between the Major Sleep Symptoms, the Severity of Obstructive Sleep Apnea, and Sleep Quality

*Frangiskos Frangopoulos[1], Savvas Zannetos[2], Ivi Nicolaou[1], Nicholas-Tiberio Economou[3], Tonia Adamide[1], Andreas Georgiou[1], Pantelis T. Nikolaidis[4], Thomas Rosemann[5], Beat Knechtle[5] and Georgia Trakada[3]**

[1] Respiratory Department, Nicosia General Hospital, Nicosia, Cyprus, [2] Health Economics and Statistics, Neapolis University, Paphos, Cyprus, [3] Division of Pulmonology, Department of Clinical Therapeutics, School of Medicine, Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece, [4] School of Health and Caring Sciences, University of West Attica, Athens, Greece, [5] Institute of Primary Care, University of Zurich, Zurich, Switzerland

OPEN ACCESS

Edited by:
Ingo Fietze,
Charité—Universitätsmedizin
Berlin, Germany

Reviewed by:
Maria Rosaria Bonsignore,
University of Palermo, Italy
Frederic Roche,
Université Jean Monnet, France

***Correspondence:**
Georgia Trakada
gtrakada@hotmail.com

Specialty section:
This article was submitted to
Sleep Disorders,
a section of the journal
Frontiers in Psychiatry

Received: 17 November 2020
Accepted: 29 January 2021
Published: 25 February 2021

Citation:
Frangopoulos F, Zannetos S, Nicolaou I, Economou N-T, Adamide T, Georgiou A, Nikolaidis PT, Rosemann T, Knechtle B and Trakada G (2021) The Complex Interaction Between the Major Sleep Symptoms, the Severity of Obstructive Sleep Apnea, and Sleep Quality. Front. Psychiatry 12:630162. doi: 10.3389/fpsyt.2021.630162

Introduction: Little information exists in the general population whether clinical presentation phenotypes of obstructive sleep apnea (OSA) differ in terms of sleep quality and comorbidities.

Aim: The purpose of our study was to assess possible differences between symptomatic and asymptomatic OSA patients concerning syndrome's severity, patients' sleep quality, and comorbidities.

Subjects and methods: First, in a nationwide, stratified, epidemiological survey, 4,118 Cypriot adult participants were interviewed about sleep habits and complaints. In the second stage of the survey, 264 randomly selected adults underwent a type III sleep study for possible OSA. Additionally, they completed the Greek version of Pittsburgh Sleep Quality Index (Gr-PSQI), Epworth Sleepiness Scale (ESS), Athens Insomnia Scale (AIS), and Hospital Anxiety and Depression Scale (HADS).

Results: From 264 enrolled participants, 155 individuals (40 females and 115 males) were first diagnosed with OSA. Among these 155 patients, 34% had ESS $\geq$ 10 and 49% AIS $\geq$ 6. One or both symptoms present categorized the individual as symptomatic (60%) and neither major symptom as asymptomatic (40%). There were no significant statistical differences (SSDs) between the two groups (symptomatic–asymptomatic) with regard to anthropometrics [age or gender; neck, abdomen, and hip circumferences; and body mass index (BMI)]. The two groups had no differences in OSA severity—as expressed by apnea–hypopnea index (AHI), oxygen desaturation index (ODI), and mean oxyhemoglobin saturation (SaO_2)—and in cardiometabolic comorbidities. Symptomatic patients expressed anxiety and depression more often than asymptomatics ($p < 0.001$) and had poorer subjective sleep quality (Gr-PSQI, $p < 0.001$). According to PSQI questionnaire, there were no SSDs regarding hours in bed and the use of sleep medications, but there were significant differences in the subjective perception of sleep quality ($p < 0.001$), sleep efficiency ($p < 0.001$), duration of sleep ($p = 0.001$), sleep

latency ($p = 0.007$), daytime dysfunction ($p < 0.001$), and finally sleep disturbances ($p < 0.001$).

Conclusion: According to our data, OSA patients reporting insomnia-like symptoms and/or sleepiness do not represent a more severe phenotype, by the classic definition of OSA, but their subjective sleep quality is compromised, causing a vicious cycle of anxiety or depression.

Keywords: obstructive sleep apnoea, sleep quality, anxiety, depression, cardiometabolic comorbidities

INTRODUCTION

Obstructive sleep apnea (OSA) is defined as a disorder of sleep presenting repetitive (either complete or partial) closure of the upper airway. These apneas and hypopneas lead to oxygen desaturation, activation of the autonomous nervous system, and micro arousals. OSA is related with increased morbidity and mortality, and literature indicates an association among OSA, hypertension, cardiovascular disease (CVD), and insulin resistance (1). OSA is a very common disorder with a great additive impact on public health. Epidemiologic data in Northern Europe estimate the prevalence of moderate and severe OSA to 23.4% in women and 49.7% in men (2). A recent epidemiologic study in the general population of Cyprus approximates the intermediate-to-high risk for OSA prevalence to be 50% in males and 18% in females (3). The increase of reported OSA prevalence over time is attributed to the obesity epidemic, the advanced polysomnographic recording techniques, and the revision of the diagnostic criteria (4). In a South American population-based epidemiologic study, 32.8% of the participants had OSA and 16.9% had an apnea–hypopnea index (AHI) $\geq$ 15. In the same study, Epworth Sleepiness Scale (ESS) $>$ 9 and/or frequencies higher than once a week of the eighth question of Pittsburgh Sleep Quality Index (PSQI) classified the participants in the 55% of the population experiencing sleepiness (5). A study in Spain recorded hypersomnolence in 18% of the subjects and was not related with OSA (6). Interestingly, a longitudinal study of the Wisconsin Sleep Cohort estimated a 3-fold greater mortality risk for participants with severe sleep-disordered breathing (SDB), independently of sleepiness (7). In a large cluster analysis, depression was the lowest (5.2%) in the group with young overweight, minimally symptomatic without comorbidities group and greater (26.4%) in the middle-aged symptomatic multimorbid OSA group (8). Even less evidences exist in the literature concerning insomnia and OSA, as initially it was not considered a symptom related to OSA. What could be the clinical importance of daytime symptoms is yet to be answered.

Several screening questionnaires have been validated to identify patients with OSA, based mainly on symptoms and demographics data. Patients often complain about sleepiness and/or insomnia-like symptoms. There is considerable variability in symptom perception and expression, biological severity, and consequences of the syndrome and sleep quality among patients, even though OSA diagnosis is usually defined by AHI.

Recent studies have suggested that this heterogeneity of OSA could be due to different phenotypes in terms of symptoms and have aimed to identify clinical subtypes of OSA, taking into account demographics, severity of disease, symptoms, and comorbidities (9–12). A pioneer study identified three groups: (a) disturbed sleep (insomnia and restless sleep), (b) minimally symptomatic, and (c) excessive sleepiness during daytime (9). Consequent studies identified similar or more specific-oriented groups. For example, a multicenter study described five clinical phenotypes: (a) disturbed sleep, (b) minimally symptomatic, (c) upper airway symptoms with sleepiness, (d) upper airway symptoms dominant, and (e) sleepiness dominant (with few other symptoms) (10). A prospective longitudinal study of adult patients with OSA (AHI of $\geq$5/h) examined four clinical presentation phenotypes considering daytime symptoms described as excessive daytime sleepiness (EDS) and nocturnal sleep problems other than OSA (insomnia): (1) EDS, (2) EDS/insomnia, (3) non-EDS/non-insomnia, (4) and insomnia phenotype (11). In another attempt to investigate treatment outcomes on different clinical phenotypes, a study identified five distinct clusters with marked clinical differences (12). Sleepiness, insomnia, and lack of symptoms are the common components of all taxonomy efforts.

Multiple subcategorizations, though interesting, minimally improve our diagnostic abilities, treatment options, progression of the syndrome, and outcome prediction. Our attempt was to investigate potential differences between two main groups: those expressing major symptoms (sleepiness and/or insomnia) and those with minimal symptoms. The latent is a silent group, difficult to identify during screening and with potentially the same harmful consequences of OSA. We designed this study in order to assess possible differences between symptomatic and asymptomatic patients, concerning the severity of the syndrome, the prevalence of comorbidities, the subjective sleep quality, and common mental disturbances, namely, anxiety and depression.

SUBJECTS AND METHOD

In a large-scale epidemiologic study conducted in the adult general population, 4,118 adult participants were interviewed in order to estimate OSA prevalence in Cyprus [Cyprus Sleep Apnea Epidemiological Study (CySAES)] (3). The initial sample consisted of adult individuals residing in Cyprus. Inclusion criteria were (1) age $\geq$ 18 years, (2) Cypriot citizens, and (3) consent to participate in the study. The sample was categorized based on the last demographic report (2016) by district, rural, or urban area; gender; and age (13). The questionnaire was

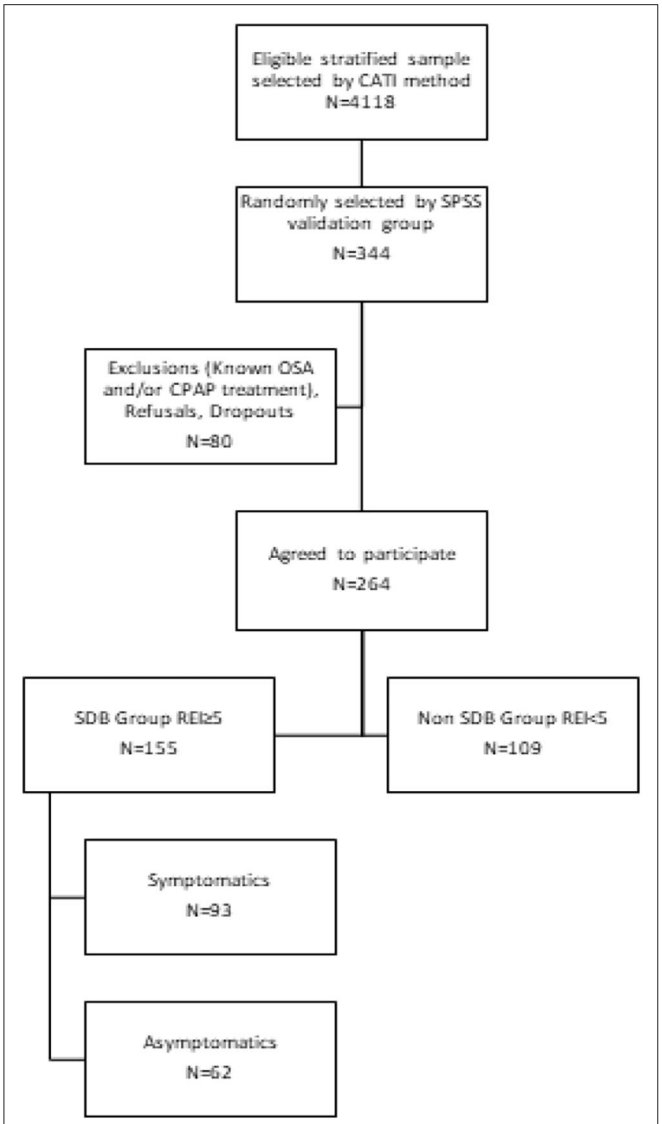

FIGURE 1 | Study selection flowchart.

administered using computer-assisted telephone interviewing (CATI) method (14). First, all eligible participants were interviewed by phone and answered a modified STOP-Bang questionnaire in order to estimate OSA risk. A secondary cross-sectional nationwide survey was piloted to examine the validity of the estimated screening results. From the initial representative sample, 344 adults were randomly selected to participate in the second stage procedure by undertaking a type III sleep study. A type III sleep testing device monitors a minimum of four channels that include one or more channels of respiratory effort, airflow, oxygen saturation, and heart rate/electrocardiogram. No strict inclusion or exclusion criteria were applied in this second phase of the study, in order to guarantee no bias in the selection, minimize the necessary sample size, and achieve reliable results. Participants were excluded from the analyses only if they had a previous known history of sleep apnea and/or were under treatment with continuous positive airway pressure (CPAP) or other therapies. The flowchart of the study is summarized in **Figure 1**.

A total of 264 adults (76.74%, age: 21–83 years) finally underwent a type III sleep study assessment for possible OSA. Standards from the American Academy of Sleep Medicine (AASM) manual were used to score respiratory events (15). The AHI was calculated as the mean number of apneas and hypopneas per hour of sleep study. AHI $\geq$ 5 was considered diagnostic for sleep apnea regardless of symptoms.

Additionally, all subjects provided a self-reported medical history about previously diagnosed comorbidities (hypertension, arrhythmias, heart failure, ischemic heart disease, previous stroke, and diabetes mellitus) and answered the Greek version of PSQI (Gr-PSQI), ESS, Athens Insomnia Scale (AIS), and Hospital Anxiety and Depression Scale (HADS).

PSQI questionnaire contains 19 self-rated questions and 5 questions rated by the bed partner or roommate. Only self-rated questions are included in the scoring. The 19 self-rated questions are combined to form 7 component scores; each one has a range of 0–3 points and represents 7 clinically derived domains of sleep difficulties. In all cases, 0 indicates no difficulty, while 3 indicates severe difficulty. The seven component scores are then summed to yield total surrogate PSQI score (global PSQI) with a range of 0–21 points, with 21 indicating severe difficulties in all areas (16). Self-administered score of >5 has a diagnostic sensitivity of 89.6% and specificity of 86.5% to distinguish "poor" sleepers from "good" sleepers, even though it is not related to objective sleep measures [actigraphy and polysomnography (PSG)] in a community sample.

ESS measures the general level of sleepiness by asking people to rate their usual chances of dozing off or falling asleep in eight different situations or activities of their daily lives. Although a score > 10 is considered affirmative for excessive, self-rated, daytime sleepiness, the correlation between ESS and mean sleep latency or measures of sleep apnea severity is low (17).

AIS is designed to assess the nature, severity, and impact of insomnia and monitor treatment response in adults. A cutoff score of $\geq$6 is used to establish the diagnosis of insomnia (18). The eradication of primary and secondary definitions of insomnia allows the clinicians to diagnose insomnia regardless of the causes of the disorder.

Finally, HADS is a reliable instrument for detecting and separating the states of depression and anxiety, by excluding somatic symptoms (19). Scores of >10 are indicative of psychological morbidity, whereas scores between 8 and 10 are considered borderline.

Known psychiatric pathologies were ruled out at the time of inclusion, by using a self-reported medical history table describing the major psychiatric and neurologic pathologies and medication that could affect the scores of the symptom questionnaires.

We divided newly diagnosed sleep apneic patients in symptomatics (Group A) and asymptomatics (Group B) in order to investigate possible differences between the

TABLE 1 | Characteristics of the SDB group participants.

Gender 1 = female 2 = male	Age	BMI	ESS	AIS	PSQI	HADS-Anxiety	HADS-Depression	AHI
2	78	31.9	4	0	4	1	2	13.2
2	65	35.8	7	15	14	8	11	45.3
2	64	28.9	2	4	5	1	3	22
2	81	23.1	1	3	5	7	5	13.3
2	57	27.4	0	0	5	1	2	20.4
2	36	30.8	10	9	7	6	8	33.2
1	58	29.5	11	7	4	4	7	38.8
2	48	30.0	9	8	4	4	7	9.4
2	69	33.3	2	3	1	7	6	18.6
1	54	29.4	8	4	5	5	2	14.1
1	63	25.0	6	4	9	3	6	6.2
1	65	34.2	4	5	6	4	1	40.1
2	66	27.0	2	1	7	2	9	86
2	65	24.0	17	2	2	6	2	14.3
1	60	29.7	3	9	6	5	5	10.5
2	55	28.7	11	4	7	6	6	30.1
1	72	32.4	4	6	6	2	2	28.9
1	67	25.2	5	3	5	7	8	28.8
1	87	45.0	10	17	7	9	6	14
2	69	35.2	2	1	3	0	0	19.4
2	66	35.2	13	6	4	3	6	42.9
1	44	24.8	10	5	5	1	0	5.1
1	64	21.3	17	2	5	1	2	30.5
2	39	28.1	8	4	7	6	5	15.4
2	52	45.0	10	10	7	6	9	58.6
2	33	25.8	7	1	5	2	0	15.6
2	67	27.4	5	6	5	5	8	6.2
2	49	28.4	5	7	6	6	2	16.1
2	53	30.9	9	7	4	3	5	14.7
2	58	24.8	5	8	9	1	1	7.7
1	54	34.4	15	5	10	7	7	24.5
2	46	25.2	7	5	4	3	5	8.9
2	59	32.5	12	11	14	14	8	13.3
2	58	40.5	6	13	9	9	13	48.2
1	65	25.4	4	4	3	4	1	1.6
2	81	22.9	2	4	6	3	1	13.3
1	68	29.7	8	20	6	16	11	7.9
2	68	38.6	14	11	13	1	6	34.4
2	72	24.2	11	4	4	6	7	15.7
2	42	34.5	19	10	18	18	17	9.3
2	43	32.6	8	10	6	0		9.8
1	36	40.3	15	14	13	15	12	27.5
1	51	30.5	17	6	8	13	7	30
1	65	36.7	7	5	2	8	4	11.5
2	71	38.8	8	7	2	0	0	40.1
2	69	23.5	2	2	2	4	13	6.4
2	58	27.5	10	1	7	10	9	7.9
1	55	44.8	21	14	13	2	2	13.2
2	66	23.7	3	4	5	6	7	10.6
2	72	38.0	16	14	9	6	11	22.1
2	63	35.2	9	17	13	10	5	36.8

(Continued)

TABLE 1 | Continued

Gender 1 = female 2 = male	Age	BMI	ESS	AIS	PSQI	HADS-Anxiety	HADS-Depression	AHI
2	60	37.2	8	1	4	3	5	9.2
2	23	34.9	4	10	8	1	4	6.4
2	56	30.3	12	9	9	1	1	14
2	43	36.1	14	1	5	1	0	8.9
2	59	32.1	2	2	6	1	0	22.8
2	75	28.4	14	11	11	12	10	7.3
2	69	30.6	2	4	6	2	2	23.1
2	49	24.1	19	5	3	4	7	5.4
2	49	27.4	2	6	6	3	5	14.2
2	51	27.2	12	12	11	9	9	8
2	46	24.7	2	2	4	3	1	6.5
1	54	36.6	5	4	3	1	7	82
2	39	26.6	9	5	4	5	2	7.2
2	68	28.3	12	10	10	5	3	44.8
2	51	27.2	17	8	8	13	9	8
2	40	31.7	6	8	7	9	10	10.9
2	57	31.9	3	2	2	1	2	23.4
2	51	33.2	16	18	13	9	8	26
1	59	32.0	18	11	7	12	8	26.7
2	24	37.2	12	12	13	12	7	9.5
2	48	23.4	7	5	5	8	4	7.6
2	76	27.4	6	5	4	2	4	14.7
2	57	29.8	7	5	8	3	1	18.8
1	49	26.8	8	9	7	9	9	5.5
2	71	30.4	2	2	2	1	0	48.1
2	33	25.2	17	15	15	4	3	9.8
2	78	24.5	0	3	4	2	0	22.6
2	34	24.8	11	5	4	6	1	8.2
2	51	21.3	8	14	13	6	2	14.9
1	50	32.0	8	4	10	4	4	10
2	73	34.9	8	9	9	1	1	27.1
1	51	38.6	17	15	11	8	6	78.7
2	37	27.8	5	10	5	7	5	32.7
1	60	33.0	6	4	7	4	2	13
1	39	23.1	5	17	7	3	3	7.9
1	64	37.2	4	6	9	14	7	10.1
1	62	24.0	15	10	10	2	6	24.6
2	38	33.9	13	2	4	1	1	5.3
2	77	32.6	14	16	16	11	13	20.8
2	51	25.3	7	3	5	1	3	8.4
1	61	33.3	0	3	5	3	2	10.4
2	71	36.3	14	7	12	3	8	44.6
1	59	24.1	20	8	7	10	10	12.5
2	56	33.8	9	13	13	8	8	9.1
2	63	28.4	8	0	3	0	0	30.7
2	44	25.0	13	16	13	3	4	13.6
2	57	28.7	14	9	13	8	2	10.5
2	46	29.1	5	10	5	9	11	11.1
2	72	19.9	8	13	17	9	9	15.3
2	53	25.5	2	0	1	0	0	5.6
2	59	26.0	12	9	7	11	9	17.8

(Continued)

TABLE 1 | Continued

Gender 1 = female 2 = male	Age	BMI	ESS	AIS	PSQI	HADS-Anxiety	HADS-Depression	AHI
2	68	33.4	4	5	4	1	1	13.6
1	56	35.6	5	10	7	8	5	7.7
2	50	25.3	8	11	7	8	4	11.4
1	61	32.4	2	5	5	8	5	12.2
2	61	26.1	20	8	6	6	0	11.7
1	77	34.7	7	4	11	0	1	33.3
2	76	24.6	1	3	4	6	5	7.6
2	54	30.4	5	1	3	0	0	17.1
1	64	33.3	4	10	12	12	5	11.9
2	47	25.9	13	7	4	3	9	11.3
2	78	31.2	1	7	7	2	2	11.2
2	21	35.6	8	3	3	3	5	15.3
2	60	21.6	5	2	3	6	8	39.3
2	68	32.2	4	3		3	1	10.3
1	54	22.7	15	3	4	9	5	10.7
2	57	36.1	9	3	8	10	5	62.8
1	54	23.7	2	1	4	5	2	5.4
2	58	32.1	18	12	11	8	11	47.1
2	74	22.8	5	3	5	3	6	15.5
2	37	27.1	11	3	4	0	4	10.1
1	55	20.4	13	9	15	10	9	13.1
2	73	30.5	8	16	16	9	8	9.2
2	69	29.8	6	15	11	6	5	18.7
2	59	25.2	9	5	6	7	3	42.5
2	59	26.4	5	5	4	2	2	19.1
2	64	29.6	4	2	5	3	4	48.4
2	52	30.7	11	10	6	1	1	31.5
2	65	24.8	3	6	3	1	1	8.4
2	50	20.7	6	5	4	6	1	5.8
2	71	28.7	6	6	9		5	9.6
2	69	26.0	9	8	12	15	13	7.4
1	73	29.7	0	6	15	2	2	7.3
2	59	36.0	13	0	0	8	2	7.6
2	32	31.1	2	1	4	3	0	11.7
2	55	26.1	2	9	10	5	7	18
1	69	23.6	5	0	4	0	0	32.8
2	37	25.4	8	2	1	4	0	7
2	52	28.7	10	1	3	2	2	6.5
2	47	25.8	5	5	7	5	1	9.6
2	39	39.4	4	6	2	3	0	5.3
2	48	23.1	4	1	5	3	1	13.3
2	68	30.5	17	3	2	0	0	17.6
2	57	32.6	15	1	2	0	0	33
2	34	25.7	9	9	6	12	9	5.5
1	60	37.0	4	9	19	6	4	13.9
2	57	47.2	2	0	3	0	0	30.3
2	59	21.2	1	2	4	3	5	9.7
1	42	35.4	3	4	3	6	5	39.8
1	49	28.2	10	15	11	13	10	14.4
2	47	37.2	4	7	3	2	5	28.1

(Continued)

TABLE 1 | Continued

Gender 1 = female 2 = male	Age	BMI	ESS	AIS	PSQI	HADS-Anxiety	HADS-Depression	AHI
2	60	40.4	12	6	5	3	3	12.5
2	53	31.1	3	4	5	15	18	8.9
1	74	26.8	7	9	10	6	10	49.7

SDB, sleep-disordered breathing; BMI, body mass index; ESS, Epworth Sleepiness Scale; AIS, Athens Insomnia Scale; PSQI, Pittsburgh Sleep Quality Index; HADS, Hospital Anxiety and Depression Scale; AHI, apnea–hypopnea index.

TABLE 2 | Anthropometrics data of the study population.

	With symptoms (Group A) (mean ± SD)	Without symptoms (Group B) (mean ± SD)
Sex, male (%)	72.9	74.35
Age (years)	55.78 ± 12.5	59.29 ± 12.77
Neck circumference (cm)	42.30 ± 4.22	41.76 ± 4.27
Hip circumference (cm)	112.8 ± 10.77	110.74 ± 10.95
Abdomen circumference (cm)	107.6 ± 15.83	104.64 ± 14.15
Body mass index (kg/m^2)	30.69 ± 5.64	28.94 ± 5.09

TABLE 3 | OSA severity in terms of respiratory indices.

Symptoms (no = 0, yes = 1)		Mean	Std. deviation
AHI	0	20.26	17.08
	1	18.89	14.19
ODI	0	14.71	15.78
	1	15.18	13.92
Mean SaO_2 (%)	0	93.92	1.73
	1	93.69	2.09

OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; ODI, oxygen desaturation index.

two groups concerning syndrome's severity, patients' sleep quality, and comorbidities. One or both symptoms (sleepiness and/or insomnia-like) present categorized the individual as symptomatic (93 individuals, 60%) and neither major symptom as asymptomatic (62 individuals, 40%).

The study protocol was approved by the Institutional Review Board of both the General Hospital in Nicosia, Cyprus, and the "Alexandra" University Hospital in Greece, and the Cyprus Bioethics Committee (EEBK/EP/2016/35). All subjects gave consent to participate in the study after appropriate information was given.

Statistical analysis included summarization of the data in tables and charts, and it was performed by using a statistical analysis software platform (IBM SPSS Statistics v.25 program). Specifically, χ^2 test was performed when comparing nominal variables, and *t*-tests were performed when comparing continuous variables. Continuous variables are summarized with means and standard deviations and compared using *t*-tests. Categorical variables are summarized using frequencies and percentages and compared among groups using chi-squared. Descriptive statistics procedures for complex survey data (chi-square) were used to examine demographic and health characteristics for all participants. Two-sided hypothesis testing was performed in order to reject or not the null hypothesis. All results reported are based on two-sided tests. Tests were adjusted for all pairwise comparisons within a row of each innermost sub-table using the Bonferroni method of correction. A $p < 0.05$ was regarded as statistically significant.

RESULTS

From 4,118 eligible responders, stratified to represent the Cypriot population, a cohort of 344 individuals—randomly selected by SPSS—were enrolled; and 264 subjects (77%) underwent type III sleep test. According to the diagnostic criteria for breathing disturbances, 155 had AHI $\geq$ 5. From these 155 (40 female and 115 male) individuals, 34% had ESS > 10 and 49% AIS $\geq$ 6. The characteristics of the sleep disturbance (SDB) group are summarized in **Table 1**. One or both symptoms present categorized the individual as symptomatic (Group A, 93 individuals, 60%) and neither major symptom as asymptomatic (Group B, 62 individuals, 40%).

Males were 72.9% of symptomatic and 74.35 of asymptomatic OSA patients. Age was 55.78 ± 12.5 in symptomatics and 59.29 ± 12.77 in asymptomatics. To ensure the internal validity of our research, the two groups were tested for confounding factors, namely, gender, age, and body mass index (BMI). There were no significant statistical differences (SSDs) between the two groups (symptomatic–asymptomatic) concerning anthropometrics (neck, abdomen, and hip circumferences; BMI; age; or gender; **Table 2**). The two groups had also no SSD in OSA severity as concluded by AHI, oxygen desaturation index (ODI), mean oxygen saturation (SaO_2), and comorbidities. Sleep test data are summarized in **Table 3**.

Sleep Quality

Symptomatics had statistically significant poorer sleep quality than asymptomatics (GR-PSQI, 8.41 ± 4.23, vs. 4.88 ± 2.43, $p = 0.000$), with no SSD regarding hours in bed (7.14 ± 1.05 vs. 7.24 ± 1.21) and the use of sleep medications (0.45 ± 1.06 vs. 0.18 ± 0.65, comp6). SSDs between OSA patients with and

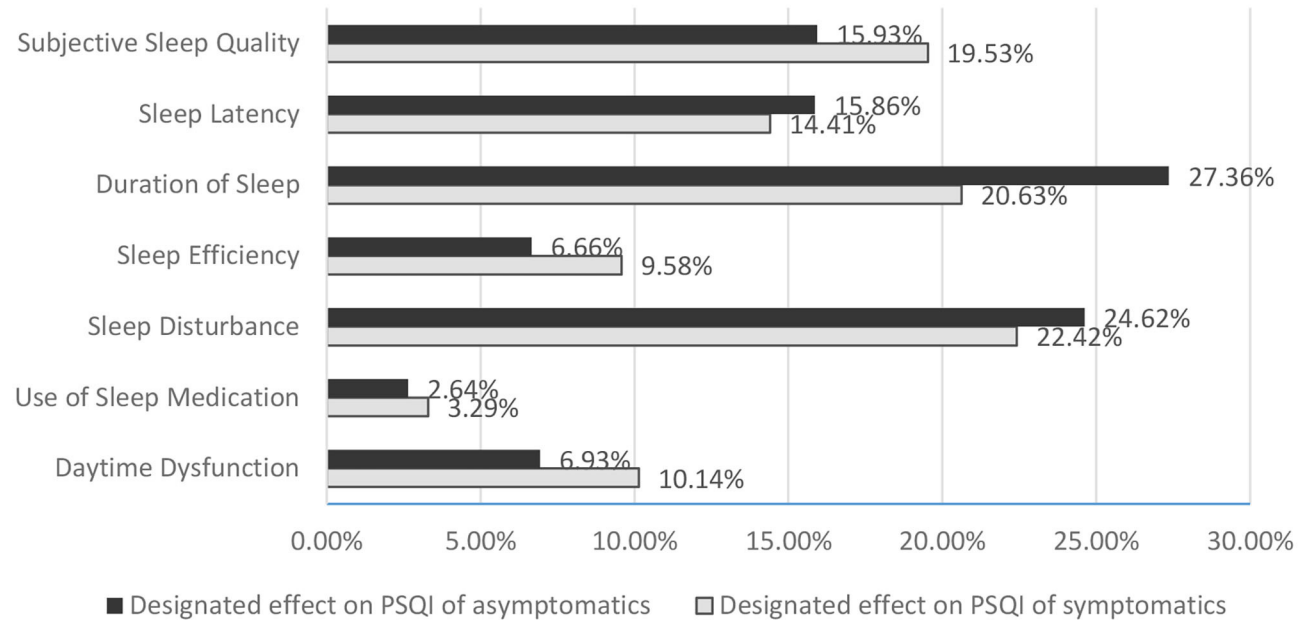

FIGURE 2 | Designated effect of categories on PSQI in OSA patients with and without symptoms. PSQI, Pittsburgh Sleep Quality Index; OSA, obstructive sleep apnea.

without symptoms were observed in the subjective perception of sleep quality (1.61 ± 0.93 vs. 0.81 ± 0.61, $p = 0.000$, comp1), sleep latency (1.28 ± 1.05 vs. 0.85 ± 0.87, $p = 0.007$, comp2), sleep duration (1.62 ± 0.94 vs. 1.18 ± 0.75, $p = 0.001$, comp3), sleep efficiency (1.07 ± 1.25 vs. 0.43 ± 0.80, $p = 0.000$, comp4), sleep disturbance (1.6 ± 0.68 vs. 1.07 ± 0.47, $p = 0.000$, comp5), and daytime dysfunction (0.79 ± 0.73 vs. 0.38 ± 0.52, $p = 0.000$, comp7).

The global PSQI score for symptomatics was mainly determined by sleep disturbance (22.42%), duration of sleep (20.63%), and subjective sleep quality (19.53%). For asymptomatics, the decisive factors were primarily duration of sleep (27.36%) and sleep disturbance (24.62%) (**Figure 2**). There was SSD only in the defining contribution of duration of sleep ($p = 0.013$) in the configuration of global PSQI between the two groups (6.20 ± 1.15 for symptomatics vs. 6.66 ± 1.19 for asymptomatics, $p = 0.049$), as no SSD was observed in sleep onset and offset and time in bed.

Finally, when OSA patients with insomnia-like symptoms were compared with the rest individuals with AHI ≥ 5, all components of PSQI were SSDs, including the use of sleep medication. On the contrary, when the sleepy group was compared with the rest individuals with AHI ≥ 5, there was no SSD for hours in bed, sleep latency, and use of medication (**Table 4**).

Anxiety–Depression–Fatigue

The prevalence and severity of anxiety, depression, and fatigue were higher in patients with symptoms.

Anxiety was present in 18.1% of symptomatic OSA patients compared with 2.9% of asymptomatics ($p = 0.003$), whereas depression was likely in 12% of symptomatic patients compared with 2.9% of asymptomatics ($p = 0.037$). Symptomatics were more anxious (6.55 ± 4.37 vs. 3.65 ± 3.01, $p = 0.000$) and more depressed (6.08 ± 3.81 vs. 3.26 ± 3.28, $p = 0.000$) than asymptomatics, according to the HADS score. No SSD of previous mental illnesses existed between the two groups (11.1% of symptomatics and 8.7% of asymptomatics). Moreover, 63.4% of symptomatics complained about fatigue vs. 30.3% of asymptomatics ($p = 0.000$), with a total score of 4.65 ± 1.61 vs. 3.16 ± 1.6 ($p = 0.000$).

We further included the possible confounder PSQI total score as a variable in our regression models; in this way, we controlled for the impact of the confounding variable. The estimated measure of association before and after adjusting for confounding was examined. The coefficient for symptomatics dropped more than 10%, when total PSQI was introduced into the model, meaning that PSQI was a confounding variable that affected anxiety ($p < 0.001$, dependent variable) in a causal relationship, as well as the symptoms ($p = 0.027$, independent variable). It was also a confounding variable related with the depression ($p < 0.001$) and symptomatic groups ($p = 0.011$).

Verification

To further support our findings, comparisons were conducted between a baseline–non-OSA population sample. Sleep quality was estimated in a control sample of 109 non-SDB subjects with normal AHI (<5/h). The control sample was not divided into symptomatics and asymptomatics, as the AHI was the controlled coefficient. The control sample was summoned after the analysis of the sleep studies (**Figure 1**). When compared with the subjects with abnormal AHI (≥5/h), there was no SSD regarding HADS,

TABLE 4 | Differences in sleep quality between insomniacs and sleepiness group.

	OSA patients with insomnia-like symptoms (mean ± SD, p)	Sleepy OSA patients (mean ± SD, p)
Category 1 Subjective sleep quality	1.85 ± 0.82	1.53 ± 0.95
Category 2 Sleep latency	1.54 ± 1.00	1.00 ± 1.02
Category 3 Duration of sleep	1.82 ± 0.97	1.62 ± 0.93
Category 4 Sleep efficiency	1.35 ± 1.28	1.04 ± 1.19
Category 5 Sleep disturbance	1.71 ± 0.63	1.64 ± 0.71
Category 6 Use of sleep medication	0.53 ± 1.14	0.54 ± 1.15
Category 7 Daytime dysfunction	0.86 ± 0.70	0.79 ± 0.77
Global PSQI	9.65 ± 3.91	8.15 ± 4.27

OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index.

TABLE 5 | Verification analysis results.

Group	No	PSQI	HADS-Anxiety	HADS-Depression
AIS ≥ 6	76	9.65 ± 3.91	7.23 ± 4.34	6.89 ± 3.72
AIS < 6	79	4.77 ± 2.4	3.81 ± 3.19	3.33 ± 3.2
ESS > 10	46	8.15 ± 4.27	6.45 ± 4.54	5.91 ± 3.93
ESS ≤ 10	109	6.15 ± 3.60	4.60 ± 3.66	4.21 ± 3.67
Both symptoms	32	10.42 ± 3.52	7.73 ± 4.54	7.33 ± 3.8
0 or 1 symptom	123	5.86 ± 3.47	4.56 ± 3.66	4.10 ± 3.56
No symptoms	65	4.88 ± 2.43	3.65 ± 3.01	3.26 ± 3.28
Only AIS ≥ 6	44	8.84 ± 4.18	6.71 ± 4.12	6.40 ± 3.64
Both symptoms	32	10.42 ± 3.52	7.73 ± 4.54	7.33 ± 3.80
Only ESS > 10	14	4.40 ± 2.30	4.35 ± 3.77	3.55 ± 2.95

PSQI, Pittsburgh Sleep Quality Index; HADS, Hospital Anxiety and Depression Scale; AIS, Athens Insomnia Scale; ESS, Epworth Sleepiness Scale.

AIS, PSQI, and all its components. The PSQI score was similar between the two groups: it was 6.33 ± 3.39 in the control group vs. 6.75 ± 3.99 in the SDB group. This reinforces the outcomes of the study, suggesting the importance of symptoms in subjective sleep quality. ESS score was significantly higher in AHI ≥ 5 group (6.26 ± 4.16 in the control group vs. 8.31 ± 5.52, $p = 0.001$). To further strengthen the clinical relevance of the results of the study, a separate analysis between subjects with AHI < 15 and AHI ≥ 15 was performed. There was no significant difference for AIS, ESS, PSQI, depression, and anxiety. An extra proof that AHI severity is almost irrelevant to the investigated parameters.

Although the AHI or REI metrics are subject to criticism nowadays, they remain the way we assess patients (20); therefore, a further classification according to the standard severity of OSA was conducted. Interestingly, only ESS was significantly higher between severe OSA and control group (6.26 ± 4.16 in the control group vs. 9.47 ± 5.32, $p = 0.007$), while insomnia, anxiety, and depression were almost evenly distributed between groups. PSQI was also insignificantly different, pointing out the importance of symptoms and not AHI in the quality of sleep. Therefore, the usual markers of OSA severity do not address efficiently the sleep quality and psychiatric consequences of the syndrome if the questionnaires centered on patient-reported symptoms are not applied. Nevertheless, the small numbers of the four groups did not allow us to extract solid results between classically determined severity groups.

The analysis was repeated by using a cutoff of 15/h, which is the current way to establish the need for treatment. There was a significant difference only for sleep efficiency (0.74 ± 1.01 in the control vs. 0.84 ± 1.23, $p = 0.005$, comp4). Interestingly, anxiety and depression had no significant difference between the two groups.

The addition of a control group in the comparison did not allow us to establish that the symptoms reported, namely, insomnia and sleepiness, are solely due to the associated OSA, as these daytime symptoms are expressions of multiple different conditions and only sleepiness in severe OSA was statistically different to the control group. Nevertheless, such an establishment was not the objective of the study. The comparison with the control group fortified the importance of symptoms in sleep quality and psychiatric disturbances, as they differ not because of AHI but of the symptoms *per se*. In this regard, the analysis of classic OSA severity markers did not help in establishing more firm OSA phenotypes, as the sample was limited.

Further verification analysis was performed; results are depicted in **Table 5**. We compared the patients from the SDB group according to their response to AIS, ESS, and both. For patients with or without insomnia, there were strong significant differences for PSQI ($p < 0.000$), anxiety ($p < 0.000$), and depression ($p < 0.000$); similar differences were recorded for patients with or without both symptoms (PSQI, $p < 0.000$; anxiety, $p < 0.000$; and depression, $p < 0.000$). For patients with sleepiness compared with patients without sleepiness, there were also SSDs for PSQI ($p < 0.005$), anxiety ($p < 0.012$), and depression ($p < 0.009$). A similar sensitivity analysis for four categories of patients, with solely sleepiness or only insomnia, both symptoms, or no symptoms, was conducted. There were significant differences for PSQI between the no symptoms group and the only insomnia group ($p < 0.000$) and the no symptoms group and the both symptoms group ($p < 0.000$), but not with the only somnolence group. In an analogous pattern, there were significant differences for anxiety between the no symptoms group and the only insomnia group ($p < 0.000$) and the no symptoms group and the both symptoms group ($p < 0.000$), but not with the only somnolence group. Similarly, for depression, there were SSDs of the no symptoms group, respectively, with the only insomnia group ($p < 0.000$) and both symptoms group ($p < 0.000$), but not the only somnolence group. The results verify the impact of major sleep symptoms to the psychiatric disturbances, primarily insomnia, but somnolence cannot be acquitted due to the small sample groups.

DISCUSSION

The concept of apnea index was first introduced by Guilleminault as a metric for sleep apnea syndromes (21). Hypopneas were officially embraced in the index in a consensus report by the AASM (22). Subsequently, a persistent argument raised concerning the cutoff level of desaturation for scoring hypopneas and the tallying of arousals following respiratory events in the severity index (respiratory disturbance index) (23). The index multiplies when lower cutoff points for hypopneas are introduced and arousals are added in the calculation. AHI is criticized for correlating weakly with endotype (underlying etiology), phenotype (symptoms and adverse outcomes), and response to treatment (23, 24). Rephrasing an elegant editorial by Levy et al. (25) AHI reflects only a metric in OSA with limited impact and meaning on a complex entity. That is why novel composite scores taking into account subjective complaints, comorbidities, and AHI (26) or integrated scores for multiple constituents of disease severity (27) gain ground in describing OSA severity. The widely accepted severity cutoffs 5, 15, and 30 per hour were used for further analysis even though they are considered invalid for clinical decision making, as they correlate poorly with symptoms, comorbidities, and outcomes (28).

It is nowadays broadly recognized that the sole calculation of the AHI is not sufficient to correctly classify our apneic patients. Furthermore, excessive daytime hypersomnolence is not associated with AHI, while insomnia is the dominant symptom of OSA. Multiple phenotypes with different clinical and demographic characteristics have been reported, as the syndrome is more complex by definition. The attempt is to enhance categorization of OSA patients, link each category to a favorable treatment option, and ultimately to accomplish precision-based medicine for OSA patients (24).

Our study intended to address some of the most important clinical questions and challenges regarding (1) whether clinical phenotyping of OSA by means of symptom expression, subjectively measured with ESS and AIS, is related to disease severity as measured by AHI or other proposed indexes and (2) whether EDS and/or insomnia-like symptoms in OSA have adverse effect on PSQI and subsequently or bilaterally neuropsychiatric disorders (NPDs). According to our data in a general population of Cyprus, OSA patients reporting insomnia-like symptoms and/or sleepiness do not represent a more severe phenotype, by the classic definition of OSA with AHI, but their subjective sleep quality is compromised, causing a vicious cycle of anxiety or depression.

The current state of knowledge indicates that the diagnosis and treatment of OSA, focusing on the number of respiratory events during sleep, are an oversimplified taxonomy (26). The complex pathophysiology, the variety of clinical presentation (e.g., daytime sleepiness, insomnia-like and mood disturbances, or minimal symptoms), and the relevant comorbidities (recognized to be highly associated with OSA, e.g., arterial hypertension) comprise a heterogeneous syndrome.

Recent concepts on differing clinical phenotypes provide opportunities for a better understanding of the syndrome. Clustering of symptoms and comorbidities allows discrimination between clinical subgroups with different characteristics. There were several attempts to identify clinical subtypes of OSA (8, 9, 11, 12, 29, 30); however, the generalizability of available data is limited due to methodological differences. Nevertheless, three generally accepted subgroups are patients with paucity of symptoms, patients with EDS, and patients with complaints of insomnia-like sleep disturbance. The conventional description of a typical OSA patient has focused on symptoms of increased daytime sleepiness; however, insomnia patients represent the dominant phenotype in clinical practice. The frequency of reported insomnia symptoms in different OSA cohorts varies between 39 and 55% (31). Not $<$ 56% in a cohort were labeled as an EDS-insomnia or insomnia phenotype (11).

Taking into account the frequent coexistence of symptoms (EDS-insomnia), we recognized the existence of two clusters of patients: one with relatively low symptom burden and another with predominant insomnia-like sleep disturbance symptoms and/or daytime sleepiness, among newly diagnosed patients with AHI $\geq$ 5, in a general population-based study. These differences in expressing or not nocturnal or diurnal symptoms may be an add on risk factor for sleep apnea severity, comorbidities, mental symptoms, and, last but not the least, sleep quality. Moreover, it is important to know whether phenotyping the patients for symptoms that are characteristic but not exclusively attributed to OSA has any clinical importance. Finally, understanding of the silent asymptomatic cluster of OSA patients is important in order to re-establish our screening tools and referral patterns. Simplification to the two most common specific OSA presentation—asymptomatic vs. symptomatic—groups is essentially sufficient to assess severity profiles and collateral consequences.

Symptoms in OSA (EDS, insomnia, depression, fatigue, etc.) are considered to be influenced by sex, age, and the presence of other comorbidities (32). In our study, there were no statistical differences between the two groups (symptomatic–asymptomatic) in terms of gender, age, or comorbidities. Actually, there were different outcomes in the literature concerning EDS and insomnia-like symptoms. Although sleepiness was linked to cardiovascular morbidity and mortality outcomes (33), it was not associated with an increase of prevalence in CVD in a large cohort (34). In another population-based, cross-sectional study, insomnia prevalence did not differ between subjects with and without OSA, but moderate-to-severe OSA subjects reported less insomnia symptoms than subjects without OSA (35). It is possible that other coexisting sleep disorders, definition, and assessment of the symptoms and the studied population also affect the results (9, 36).

PSG is the reference assessment tool for the diagnosis of OSA (20). Cumulative data demonstrated a weak relationship between daytime excessive sleepiness and the conventional measures of OSA severity (e.g., the AHI), and that was also confirmed in our results. The two groups—symptomatic vs. asymptomatic—had no differences in terms of AHI, ODI, and mean SaO_2 magnitude. Patients with a high AHI may score low on symptom scales and vice versa (37). This diversity may be attributed to differences in individual susceptibility to the systemic effects of OSA. The clinical definition of OSA based on the combination of AHI

and daytime symptoms is compromised by the high prevalence of elevated AHI in the general population and by the poor correlation of EDS with AHI (38). Type III studies do not include sleep staging and are expected to give a lower AHI compared with the calculation based on PSG where periods of wakefulness during the sleep study are excluded in the calculation of AHI (39). Underestimation of AHI did not affect our results, as the dependent factor was symptoms and both groups were subject to the same bias.

However, our symptomatic group reported poorer sleep quality on PSQI and complained more often about symptoms of depression, anxiety, and fatigue than did the asymptomatic group. The global PSQI score for symptomatics was mainly determined by sleep disturbance, duration of sleep, and subjective sleep quality, whereas for asymptomatics, the decisive factors were primarily duration of sleep and sleep disturbance.

Duration of sleep was less for symptomatics than for asymptomatics and the best predictor of subjective sleep quality, but there was no SSD on time in bed. Wake after sleep onset (WASO) time is not reflected on PSQI calculation, but in our opinion, it is an important sleep quality factor. In a sleep quality study in renal transplant patients, the patients with PSQI $>$ 5 were consider as poor sleepers and showed a higher total medical comorbidity score, poorer mental health, and more severe anxiety but no difference in depressive symptoms when compared with the good sleepers group (40). In another sleep quality study, subjective sleep quality was strongly negative correlated with depression score, physical symptoms, and trait anxiety (41), similar to our results. Subjective sleep quality's association with sleep onset latency was stronger than with sleep duration. In a community-dwelling adults study, with mean PSQI score of 6.3, PSQI and ESS were related poorly with each other. Participants grouped by either cluster analysis of PSQI and ESS scores differed from each other on psychological/stress symptoms, but not on polysomnographic indices. Higher PSQI scores were associated with greater psychological distress and larger sleep disturbance on sleep diaries. Finally, the PSQI was more closely related to psychological symptom ratings and sleep diary measures than the ESS (42).

Poor sleep quality has a major long-term impact on mental and physical health. Our study identified a cause-and-effect relationship between PSQI and symptoms of anxiety and depression. PSQI had a causal relation to the symptoms, especially insomnia; and symptoms' expression correlated with poor sleep quality and separately with anxiety and depression. There is growing evidence for an increased frequency of OSA in a variety of NPDs, including stroke, neurodegenerative/muscular disorders, major depression, and post-traumatic stress disorder (43, 44). Several studies suggest that OSA not only may be frequent but also represents an independent risk factor for the subsequent development of NPDs, such as depression (45).

AHI was not related to the risk for hospitalization for depression in a study by Kendzerska et al. (46), and a causal link between OSA and severe depression was not supported. Nevertheless, higher depressive symptoms were reported in OSA patients (47), almost doubled in prevalence for the OSA group compared with the no-OSA group in a population-based study (48). About 17% of OSA patients had a major depressive disorder in a large community sample (49) and up to 40% in clinical samples (47, 50). Moreover, a large general population study found an association between EDS, rather than OSA *per se*, and depression (51) and introduced symptoms in the equation. Association between OSA and depressive symptoms is questioned, but findings indicate that depression is a consequence of OSA (52, 53), and major sleep-related symptoms may be the mediators in this relation. Correction for confounders for depression like obesity, young age, female sex, and hypnotic medication use was not applied, as there were no SSDs between groups for these characteristics.

AHI proved once more a convenient metric but with limited clinical implications. The results of our study suggest that patients with depression should be routinely questioned for symptoms of insomnia and/or sleepiness, as further assessment and treatment for sleep-disordered breathing may mitigate depressive symptoms. The effects of OSA treatment in depression and anxiety especially in the symptomatic phenotype have to be assessed.

The major strength of our research is the validity of our findings, which is documented by the large representative population-based sample size and by the high response rate. This allows us to generalize the results, enabling extrapolation of findings to the original population. Moreover, we included all adult age groups, from 18+ to 80+ years old. Another major advantage of our study is the community-based, randomly selected sample that is optimal for epidemiological studies. As subjects were recruited from the community and not from clinical sleep canters, there is no referral bias, causing a spurious association of OSA with risk of comorbidities. The study identified a sleep lab-naive sample; and as OSA patients were excluded from the study, a better assessment of the natural history of untreated OSA is possible. A strength of our study is also the application of common questionnaires and simple phenotyping methodology across a population-based sample. Our study did not include all possible symptoms and comorbidities nor complicated phenotyping but only focused on major sleep symptoms that may occur in patients with OSA. This simplification in two groups minimizes the need for a larger sample to support SSD. Moreover, most of the previous studies included patients with moderate-to-severe OSA, and the clusters found may not be generalizable to patients with milder OSA. An important feature of our study is that all individuals with AHI $\geq$ 5 were introduced in the study. Reflecting the established demographic risk factors for OSA, the cohort was generally middle-aged, moderately obese, and predominantly male.

Limitations must also be acknowledged. A self-reported questionnaire concerning the history of comorbid diseases was assembled, but no medical assessment was provided in those with a negative history in order to identify non-diagnosed comorbidities. Another limitation is the absence of a psychiatric revision of the participants according to their self-reported mental questionnaires. Any differences with previous reports may be attributed to cultural or regional differences in symptom reporting (54, 55) or referral strategies and access to care,

together with existing known variation in OSA etiology across ethnic groups (56–60).

As Young stated, there is more to be done in the quantification of the adverse health consequences of OSA in order to define the overall social burden (61). Experts recognizing the poor correlation between AHI and daytime symptoms, as well the multivariate expression of the syndrome, advised a revision of the diagnostic criteria and severity thresholds for OSA, taking into consideration the different clinical and pathophysiological phenotypes and relevant comorbidities (26). To conclude, identification of two distinct groups according to the expressed daytime symptoms, symptomatics and asymptomatics, requires future surveys concerning diagnostic screening, consequences, and effective treatments.

CONCLUSION

According to our study, OSA patients reporting insomnia and or sleepiness do not represent a more severe phenotype as to the classic taxonomy of syndrome's gravity categorized by the number of apneas and hypopneas per hour of sleep. Neither do symptomatics report a greater number of comorbidities. Nevertheless, symptomatics express poor sleep quality and mood disturbances significantly different from asymptomatics. The explanation given is that their sleep quality is compromised, causing a vicious cycle of anxiety or depression.

The results of the study indicate that the severity of the sleep respiratory pathology represented by AHI is inadequate. Even with the addition of oxygenation indices for the cardiovascular manifestations of the syndrome as we demonstrated in a previous study (62) and the daytime symptoms as we proposed in this study, one is uncertain to suggest a novel classification, as there are more elements missing. Nevertheless, objective assessment using symptom questionnaires is in our opinion essential and should be compulsory, as they illuminate the sleep quality aspect and predisposition for psychic imbalance.

This study contributes to the understanding of the impact of EDS and insomnia in OSA. According to our results, we ought to reconsider our screening techniques, customized to the patient's complaints, probably with the utility of sleep quality questionnaires and screening tools for NPDs. Moreover, it will be desirable to validate clinical assessment methods that correctly classify a new OSA patient. This understanding could enhance personalized treatment approaches in OSA patients. Finally, a new conceptual framework to evaluate disease severity of OSA may be developed. The diagnostic workup should incorporate this multifactorial approach and define severity, not only considering AHI but also including EDS, NPDs (e.g., cognitive impairment and depression), related sleep disturbances (e.g., insomnia), consequences, and prognoses.

A confirmation of the current findings in longitudinal studies would be needed to more precisely evaluate the value of defining clinical presentation phenotype.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the study protocol was approved by the Institutional Review Board of both the General Hospital in Nicosia, Cyprus and the Alexandra University Hospital, in Greece and the Cyprus Bioethics Committee (EEBK/EP/2016/35). All subjects gave consent to participate in the study after appropriate information was given. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IN and TA contributed in the acquisition of the data. N-TE conceived and designed the study. SZ performed the data analysis. FF wrote the paper. GT, PN, TR, and BK participated in the interpretation of the data and revised them critically for content. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Allan I. Pack advances in sleep-disordered breathing. *Am J Respir Crit Care Med.* (2006) 173:7–15. doi: 10.1164/rccm.200509-1478OE
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the hypnolaus study. *Lancet Respir Med.* (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
3. Frangopoulos F, Nicolaou I, Zannetos S, Economou NT, Adamide T, Georgiou A, et al. Estimating obstructive sleep apnea in Cyprus: a randomised, stratified epidemiological study using STOP-Bang sleep apnea questionnaire. *Sleep Med.* (2019) 61:37–43. doi: 10.1016/j.sleep.2019.04.013
4. Senaratna CV, Perret JL, Lodge C, Lowe A, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev*. (2016) 34:70–81. doi: 10.1016/j.smrv.2016.07.002
5. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the saò paulo epidemiologic sleep study. *Sleep Med.* (2010) 11:441–6. doi: 10.1016/j.sleep.2009.10.005
6. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea–hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 Yr. *Am J Respir Crit Care Med.* (2001) 163:685–9. doi: 10.1164/ajrccm.163.3.2005065
7. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the wisconsin sleep cohort. *Sleep*. (2008) 31:1071–8.
8. Bailly S, Destors M, Grillet Y, Richard P, Stach B, Vivodtzev I, et al. Obstructive sleep apnea: a cluster analysis at time of diagnosis. *PLoS ONE*. (2016) 11:e0157318. doi: 10.1371/journal.pone.0157318
9. Ye L, Pien GW, Ratcliffe SJ, Björnsdottir E, Arnardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J.* (2014) 44:1600–7. doi: 10.1183/09031936.00032314
10. Keenan BT, Kim J, Singh B, Bittencourt L, Chen NH, Cistulli PA, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep J.* (2018) 41:zsx214. doi: 10.1093/sleep/zsx214

11. Saaresranta T, Hedner J, Bonsignore MR, Riha RL, McNicholas WT, Penzel T, et al. Clinical phenotypes and comorbidity in European sleep apnoea patients. *PLoS ONE.* (2016). 11:e0163439. doi: 10.1371/journal.pone.0163439
12. Gagnadoux F, Le Vaillant M, Paris A, Pigeanne T, Leclair-Visonneau L, Bizieux-Thaminy A, et al. Relationship between OSA clinical phenotypes and CPAP treatment outcomes. *Chest*. (2016). 149:288–90. doi: 10.1016/j.chest.2015.09.032
13. Tyrer S, Heyman B. Sampling in epidemiological research: issues, hazards and pitfalls. *BJPsych Bull.* (2016) 40:57–60. doi: 10.1192/pb.bp.114.050203
14. Kempf AM, Remington PL. New challenges for telephone survey research in the twenty-first century. *Annu Rev Public Health.* (2007) 28:113–26. doi: 10.1146/annurev.publhealth.28.021406.144059
15. Iber C. *American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. Westchester, IL: American Academy of Sleep Medicine.(2007).
16. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The pittsburg sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1988) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
17. Johns MW. A new method for measuring daytime sleepiness: the epworth sleepiness scale. *Sleep.* (1991) 14:540–5. doi: 10.1093/sleep/14.6.540
18. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the athens insomnia scale. *J Psychosom Res.* (2002) 55:263–7. doi: 10.1016/S0022-3999(02)00604-9
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x
20. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an american academy of sleep medicine clinical practice guideline. *J Clin Sleep Med.* (2017) 13:479–504. doi: 10.5664/jcsm.6506
21. Guilleminault C, Van Den Hoed J, Mitler M. Clinical overview of the sleep apnea syndromes. In: Guilleminault C, Dement W, editors. *Sleep Apnea Syndromes*. New York, NY: Alan R Liss (1978). p. 1–12.
22. The Report of an American Academy of Sleep Medicine TaskForce. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. (1999) 22:667–89. doi: 10.1093/sleep/22.5.667
23. Pevernagie DA, Gnidovec-Strazisar B, Grote L, Heinzer R, McNicholas WT, Penzel T, et al. On the rise and fall of the apnea–hypopnea index: a historical review and critical appraisal. *J Sleep Res.* (2020) 29:e13066. doi: 10.1111/jsr.13066
24. Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. *Am J Respir Crit Care Med.* (2019) 200:691–703. doi: 10.1164/rccm.201901-0014TR
25. Lévy P, Tamisier R, Pépin JL. Assessment of sleep-disordered-breathing: quest for a metric or search for meaning? *J Sleep Res.* (2020) 29:e1314. doi: 10.1111/jsr.13143
26. Randerath W, Bassetti CL, Bonsignore MR, Farre R, Ferini-Strambi L, Grote L, 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) 52:1702616. doi: 10.1183/13993003.02616-2017
27. Dieltjens M, Verbraecken JA, Hedner J, Vanderveken OM, Steiropoulos P, Kvamme JA. Use of the clinical global impression scale in sleep apnea patients –results from the ESADA database. *Sleep Med.* (2019) 59:56–65. doi: 10.1016/j.sleep.2018.10.028
28. Hudgel DW. Sleep apnea severity classification-revisited. *Sleep*. (2016) 39:1165–6. doi: 10.5665/sleep.5776
29. Vavougios GD, George DG, Pastaka C, Zarogiannis SG, Gourgoulianis KI. Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. *J Sleep Res.* (2016) 25:31–8. doi: 10.1111/jsr.12344
30. Lacedonia D, Carpagnano GE, Sabato R, Lo Storto MM, Palmiotti GA, Capozzi V, et al. Characterization of obstructive sleep apnea-hypopnea syndrome (OSA) population by means of cluster analysis. *J Sleep Res.* (2016) 25:724–30. doi: 10.1111/jsr.12429
31. Luyster FS, Buysse DJ, Strollo PJ Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med*. (2010). 6:196–204. doi: 10.5664/jcsm.27772
32. Levy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers.* (2015) 1:15015. doi: 10.1038/nrdp.2015.15
33. Ren R, Li Y, Zhang J, Zhang J, Zhou J, Sun Y, et al. Obstructive sleep apnea with objective daytime sleepiness is associated with hypertension. *Hypertension.* (2016) 68:1264–70. doi: 10.1161/HYPERTENSIONAHA.115.06941
34. Oglivie RP, Lakshminarayan K, Iber C, Patel SR, Lutsey PL. Joint effects of OSA and self-reported sleepiness on incident CHD and stroke. *Sleep Med.* (2018) 44:32–7. doi: 10.1016/j.sleep.2018.01.004
35. Uhlig BL, Hagen K, Stjern EM, Gravdahl GB, Sand T. The relationship between obstructive sleep apnea and insomnia: a population-based cross sectional polysombographic study. *Sleep Med.* (2019) 54:126–33. doi: 10.1016/j.sleep.2018.10.026
36. Adams RJ, Appleton SL, Vakulin A, Lang C, Martin SA, Taylor AW, et al. Association of daytime sleepiness with obstructive sleep apnoea and comorbidities varies by sleepiness definition in a population cohort of men. *Respirology.* (2016) 21:1314–21. doi: 10.1111/resp.12829
37. Deegan PC, McNicholas WT. Predictive value of clinical features for the obstructive sleep apnoea syndrome. *Eur Respir J.* (1996) 9:117–24. doi: 10.1183/09031936.96.09010117
38. Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T. Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. *Eur Respir J.* (2016) 47:194–202. doi: 10.1183/13993003.01148-2015
39. Escourrou P, Grote L, Penzel T, McNicholas WT, Verbraecken J, Tkacova R, et al. The diagnostic method has a strong influence on classification of obstructive sleep apnea. *J Sleep Res.* (2015) 24:730–8. doi: 10.1111/jsr.12318
40. Kachuee H, Ameli J, Taheri S, Assari S, Riahipour F, Khedmat H, et al. Sleep Quality and its correlates in renal transplant patients. *Transpant Proc.* (2007) 39:1095–7. doi: 10.1016/j.transproceed.2007.04.001
41. Augner C. Association of subjective sleep quality with depression score, anxiety. Physical symptoms and sleep onset latency in students. *Cenr Eur J Public Health.* (2011) 19:115–7. doi: 10.21101/cejph.a3647
42. Buysse DJ, Hall ML, Strollo PJ, Kamarck TW, Owens J, Lee L, et al. Relationships between the pittsburgh sleep quality index (PSQI), epworth sleepiness scale (ESS), and clinical/polysomnographic measures in a community sample. *J Clin Sleep Med.* (2008) 4:563–71. doi: 10.5664/jcsm.27351
43. Gupta M, Simpson FC. Obstructive sleep apnea and psychiatric disorders: a systematic review. *J Clin Sleep Med.* (2015) 11:165–75. doi: 10.5664/jcsm.4466
44. Knechtle B, Economou NT, Nikolaidis PT, Velentza L, Kallianos A, Steiropoulos P, et al. Clinical characteristics of obstructive sleep apnea in psychiatric disease. *J Clin Med.* (2019) 8:534. doi: 10.3390/jcm8040534
45. Haba-Rubio J, Marti-Soler H, Tobback N, Andries D, Marques-Vidal P, Waeber G, et al. Sleep characteristics and cognitive impairment in the general population: the hypnolaus study. *Neurology.* (2017) 88:463–9. doi: 10.1212/WNL.0000000000003557
46. Kendzerska T, Gershon AS, Hawker GA, Tomlinson GA, Leung RS. Obstructive sleep apnoea is not a risk factor for incident hospitalised depression: a historical cohort study. *Eur Respir J.* (2017) 49:1601361. doi: 10.1183/13993003.01361-2016
47. Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. *Sleep Med Rev.* (2009) 13:437–44. doi: 10.1016/j.smrv.2009.04.001
48. Chen YH, Keller JK, Kang JH, Hsieh HJ, Lin HC. Obstructive sleep apnea and the subsequent risk of depressive disorder: a population-based follow-up study. *J Clin Sleep Med.* (2013) 9:417–23. doi: 10.5664/jcsm.2652
49. Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. *J Clin Psychiatry.* (2003) 64:1195–00. doi: 10.4088/JCP.v64n1009
50. Basta M, Lin HM, Pejovic S, Sarrigiannidis A, Bixler EO, Vgontzas AN. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: sex differences. *J Clin Sleep Med.* (2008) 4:19–25. doi: 10.5664/jcsm.27074

51. LaGrotte C, Fernandez-Mendoza J, Calhoun SL, Liao D, Bixler EO, Vgontzas AN. The relative association of obstructive sleep apnea, obesity and excessive daytime sleepiness with incident depression: a longitudinal, population-based study. *Int J Obes.* (2016) 40:1397–404. doi: 10.1038/ijo.2016.87
52. Bixler EO, Gaines J, Vgontzas AV. Obstructive sleep apnoea and depression: is there an association? *Eur Respir J.* (2017) 49:1700858. doi: 10.1183/13993003.00858-2017
53. Kales A, Caldwell AB, Cadieux RJ, Soldatos CR, Kales JD. Severe obstructive sleep apnea–II: associated psychopathology and psychosocial consequences. *J Chronic Dis.* (1985) 38:427–34. doi: 10.1016/0021-9681(85)90138-9
54. Im EO, Ko Y, Chee W. Symptom clusters among multiethnic groups of cancer patients with pain. *Palliat Support Care.* (2013) 11:295–305. doi: 10.1017/S1478951512000314
55. Bauer AM, Chen CN, Alegría M. Prevalence of physical symptoms and their association with race/ethnicity and acculturation in the United States. *Gen Hosp Psychiatry.* (2012) 34:323–31. doi: 10.1016/j.genhosppsych.2012.02.007
56. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spryet K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *Am J Respir Crit Care Med.* (1997) 155:186–92. doi: 10.1164/ajrccm.155.1.9001310
57. Ong KC, Clerk AA. Comparison of the severity of sleep-disordered breathing in Asian and Caucasian patients seen at a sleep disorders center. *Respir Med.* (1998) 92:843–8. doi: 10.1016/S0954-6111(98)90386-9
58. Li KK, Kushida C, Powell NB, Riley RW, Guilleminaultet C. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. *Laryngoscope.* (2000) 110(10 Pt 1):1689–93. doi: 10.1097/00005537-200010000-00022
59. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler A, et al. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. *Sleep.* (2010) 33:1075–80. doi: 10.1093/sleep/33.8.1075
60. O'Connor GT, Lind BK, Lee ET, Nieto FJ, Redline S, Samet JM, et al. Variation in symptoms of sleep-disordered breathing with race and ethnicity: the sleep heart health study. *Sleep*. (2003). 26:74–9.
61. Young T. Rationale, design and findings from the Wisconsin sleep cohort study: toward understanding the total societal burden of sleep disordered breathing. *Sleep Med Clin.* (2009) 4:37–46. doi: 10.1016/j.jsmc.2008.11.003
62. Frangopoulos F, Nicolaou I, Zannetos S, Economou NT, Adamide T, Trakada G. Association between respiratory sleep indices and cardiovascular disease in sleep apnea—a community-based study in cyprus. *J Clin Med.* (2020) 9:2475. doi: 10.3390/jcm9082475

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 February 2021
doi: 10.3389/fneur.2021.598632

Sleep Spindle Characteristics in Obstructive Sleep Apnea Syndrome (OSAS)

Hiwa Mohammadi[1,2,3], *Ardalan Aarabi*[4,5], *Mohammad Rezaei*[1,6], *Habibolah Khazaie*[1] and *Serge Brand*[1,7,8,9,10]*

[1] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran, [2] Department of Neurology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran, [3] Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran, [4] Laboratory of Functional Neuroscience and Pathologies (LNFP, EA4559), University Research Center (CURS), University Hospital of Amiens, Amiens, France, [5] Faculty of Medicine, University of Picardie Jules Verne, Amiens, France, [6] Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran, [7] University of Basel, Psychiatric Clinics (UPK), Center for Affective, Stress and Sleep Disorders (ZASS), Basel, Switzerland, [8] Department of Sport, Exercise and Health, Division of Sport Science and Psychosocial Health, University of Basel, Basel, Switzerland, [9] Substance Abuse Prevention Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran, [10] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

OPEN ACCESS

Edited by:
Liborio Parrino,
University of Parma, Italy

Reviewed by:
Axel Steiger,
Ludwig Maximilian University of Munich, Germany
Rogerio Santos-Silva,
Núcleo Interdisciplinar da Ciência do Sono (NICS), Brazil

***Correspondence:**
Serge Brand
serge.brand@upk.ch

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Neurology

Received: *27 August 2020*
Accepted: *21 January 2021*
Published: *25 February 2021*

Citation:
Mohammadi H, Aarabi A, Rezaei M, Khazaie H and Brand S (2021) Sleep Spindle Characteristics in Obstructive Sleep Apnea Syndrome (OSAS). Front. Neurol. 12:598632. doi: 10.3389/fneur.2021.598632

Background: We compared the density and duration of sleep spindles topographically in stage 2 and 3 of non-rapid eye movement sleep (N2 and N3) among adults diagnosed with Obstructive Sleep Apnea Syndrome (OSAS) and healthy controls.

Materials and Methods: Thirty-one individuals with OSAS (mean age: 48.50 years) and 23 healthy controls took part in the study. All participants underwent a whole night polysomnography. Additionally, those with OSAS were divided into mild, moderate and severe cases of OSAS.

Results: For N2, sleep spindle density did not significantly differ between participants with and without OSAS, or among those with mild, moderate and severe OSAS. For N3, *post-hoc* analyses revealed significantly higher spindle densities in healthy controls and individuals with mild OSAS than in those with moderate or severe OSAS. Last, in N2 a higher AHI was associated with a shorter sleep spindle duration.

Conclusion: OSAS is associated with a significantly lower spindle density in N3 and a shorter spindle duration in N2. Our results also revealed that, in contrast to moderate and severe OSAS, the sleep spindle characteristics of individuals with mild OSAS were very similar to those of healthy controls.

Keywords: spindle density, spindle duration, obstructive sleep apnea syndrome, N2, N3 apnea/hypopnea index

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is one of the most common breathing-related sleep disorders. The American Academy of Sleep Medicine (1) defines OSAS as repetitive episodes of complete or partial upper airway obstruction during sleep. Such complete or partial upper airway obstructions lead to a reduced blood oxygen saturation with brief arousals. Further, OSAS is

diagnosed based on the patient complaints of daytime sleepiness, non-restorative sleep, fatigue or insomnia symptoms, along with awakening of sleep with breath holding, gasping or choking, and with their report of habitual snoring and/or breathing interruptions. Next, polysomnographic analyses (PSG) show five or more predominantly obstructive respiratory events [(obstructive and mixed apneas, hypopneas or respiratory effort-related arousals (RERAs)]. Relatedly, OSAS is diagnosed, if PSG analyses record 15 or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs) per hour (1).

As regards prevalence rates of OSAS, a meta-analysis reported the following figures: 3% of women, and 10% of men aged 30 to 49 years suffer from moderate to severe OSAS; 9% of women, and 17% of men aged 50 to 70 years suffer from moderate to severe OSA (2). Population-based studies reported prevalence rates of 23.4% for women and 49.7% for men (3, 4).

Obstructive sleep apnea syndrome is not only associated with a reduced sleep efficiency, but also with a lower quality of life (5) and an increased risk of systemic comorbidities such as cardiovascular diseases, hypertension, and metabolic syndrome (6–8). Relatedly, the most important epidemiological risk factors for OSAS are obesity and male gender (9, 10). In addition, higher OSAS is associated with a decreased cognitive executive performance and memory consolidation (11), with early changes in biomarkers for Alzheimer's Disease (12), and with the hypoactivation of brain regions associated with cognition (13, 14).

Within the broad range of encephalographic and sleep-related signals, sleep spindles are understood as 0.5 to 3 s episodes of 9–16 Hz electroencephalogram oscillations resulting from the intra-thalamic network of nucleus *Reticularis thalami* (nRt) and thalamocortical neurons during non-rapid eye movement (nREM) sleep (15–18). Sleep spindles are well-known as neurophysiological underpinnings of stage 2 nREM sleep (N2), but they can also occur in stage 3 nREM sleep (N3) (19).

Sleep spindles have attracted increased attention for their associations with cognitive, emotional and social processes: Sleep spindle activities are associated with neural structures and functions (20); it follows that sleep spindles are considered an important index both for typically developing neurocognitive processes and for sleep disorders (21, 22). To illustrate, a higher sleep spindle density was associated with increased memory consolidation (23), motor development, language abilities, learning, and cognitive performance (24). Among preschoolers, a higher spindle density predicted current and future cognitive-emotional and social skills (25–27). In contrast, a lower sleep spindle activity is observed among older individuals with dementia (28).

The pattern of sleep spindle indices among individuals with OSAS is inconsistent. As regards the assessment of sleep spindles, both visual and automatic spindle detection methods are used, along with spectral analysis techniques for detecting sigma band frequencies, either separately or in combination. In some studies individuals with OSAS had statistically similar patterns of spindle density and sigma power, compared to controls (29). In contrast, individuals with OSAS had a lower spindle density, slower spindle frequency, and lower sigma power, compared to healthy control (30–34).

As regards sleep stages, studies reported significant differences in sleep spindle characteristics between individuals with and without OSAS during all NREM stages but not during REM (33, 35, 36). Himanen et al. (37) observed an increased spindle frequency at the end of the night among healthy controls, but not among individuals with OSAS. Some studies reported significant differences in spindle characteristics between the two groups in REM sleep (38).

In children and adolescents, a lower spindle density in N2 but not in N3 was observed in children with mild OSAS, when compared to healthy controls (39). In contrast, Madaeva et al. (40) used a automatized software for sleep spindle detection and reported higher levels of spindles and spindle density, but a lower spindle amplitude and frequency during N2 in overweight adolescents with OSAS, compared to overweight or normal weight adolescents with no OSAS. No differences were observed for spindle duration between overweight adolescents with and without OSAS, and normal weight adolescents (40).

Last, spindle activity increases when OSAS is treated with positive airway pressure therapy (41–43). This effect could be understood as a normalization of sleep continuity, sleep architecture and sleep spindle activity in individuals with OSAS and treated with this therapy.

The pattern of mixed and inconclusive results noted above may reflect variations in sample sizes, age ranges, and different clinical criteria for recruiting and assessing participants, together with different methodologies of spindle detection at different sleep stages, and different outcome variables such as sigma band power, total number of spindles, spindle density and spindle duration.

Sleep spindles protect sleep from arousal-induced incidents, that is to say: Thalamocortical neuronal activation during spindle oscillations filters external sensory inputs to the neocortex and increases the threshold for response to external stimuli (15). Conversely, OSAS is likely to produce arousal as an internal arousal inducer, to disrupt sleep continuity and to lead to fragmented sleep. Given that both OSAS and lower sleep spindle activity were associated with a reduced memory consolidation (11, 23, 24), it is possible that the degradation of sleep spindles activity is responsible for the negative effects of OSAS on memory and cognition.

To summarize, the findings reported above do not allow to draw a uniform and coherent frame of association between OSAS and sleep spindle activity. Given this background, the aim of the present study was to shedding some further light on the associations between OSAS and sleep spindles. To this end, we analyzed the sleep spindle activity among individuals with mild, moderate and severe OSAS, and among healthy controls. We hypothesized that the spindle density and duration would differ between individuals with mild, moderate and severe OSAS, and compared to controls. Specifically, we expected that with higher OSAS sleep spindle patterns (spindle density and spindle duration) would be more impaired. The present study expands upon most previous work in that we also assessed individuals with severe OSAS. Further, there have been few studies of

spindle duration, and the present study offers an opportunity to clarify the role of the spindle duration and its interaction with spindle density during both N2 and N3 stages. The present results could have clinical importance because individuals with OSAS are at increased risk of neurocognitive impairments and this may be at least partially explained by a deterioration in sleep spindle activity. The results from this study could also be important for practical reasons: Treating OSAS may also improve sleep spindle activities, resulting in improved behavior and cognitive performance.

MATERIALS AND METHODS

Sample and Procedure

Individuals with OSAS and age-, sex-, and BMI-matched controls were invited to participate at the present study. Participants were fully informed about the aims of the study and the confidential data handling. Thereafter, they all signed the written informed consent. All participants underwent a thorough medical examination, and their sleep was objectively assessed via polysomnography. Sleep assessments took place at the Sleep Disorders Research Center (SDRC) of Kermanshah University of Medical Sciences (KUMS) between 2013 and 2016. The ethical committee of the Kermanshah University of Medical Sciences (KUMS, Kermanshah, Iran; code: KUMS.REC.1395.337) approved the study, which was performed in accordance with the ethical principles laid down in the seventh and current edition (44) of the Declaration of Helsinki.

Samples

Individuals With Obstructive Sleep Apnea Syndrome (OSAS)

A total of 31 individuals with OSAS were enrolled in the study (mean age: 49.41 years, SD = 8.96; age range: 33–59 years; 84% males). Inclusion criteria were: (1) Age between 18 and 65 years; (2) Breathing-related sleep complaints, as assessed via a thorough clinical interview and based on polysomnographic data; (3) Compliance with the study conditions such as undergoing overnight polysomnography at the sleep research center; (4) Signed written informed consent. Exclusion criteria were: (1) Current severe psychiatric issues such as acute suicidality, acute psychosis, or severe substance use disorder (opium, alcohol, cannabis, amphetamines, methamphetamines; medications); (2) Severe chronic neurological or cardiovascular issues; (3) Unwilling or unable to comply with the study conditions. (4) Unable or unwilling to withdraw from sleep-altering medications (narcotics, antihistamines, etc.) 2 weeks before the polysomnographic assessment; (5) Periodic limb movements of sleep; (6) Shift work; (7) Female participants: currently pregnant or breastfeeding.

Healthy Controls

A total of 23 individuals without any kind of sleep disturbances were enrolled in the study (mean age: 45.17 years, SD = 10.73; age range: 34–56 years; 70% males). Inclusion criteria were: (1) Age between 18 and 65 years; (2) No sleep complaints, and above all no breathing-related sleep complaints, as assessed via a thorough clinical interview and based on polysomnographic data; (3) Compliance with the study conditions such as undergoing overnight polysomnography at the sleep research center; (4) Signed written informed consent. Exclusion criteria were identical to the exclusion criteria of individuals with OSAS.

Detailed Data Collection

Participants were invited to the SDRC sleep laboratory (Kermanshah, Iran). They were advised not to have any coffee, tea, a heavy diet or a cigarette and not to snooze or sleep during the day. They were asked to arrive at the laboratory at 9 p.m. Then, they completed a short demographic questionnaire including age and sex, employee conditions, smoking, shift work; thereafter, their height and weight were measured by an experienced technician. Next, the PSG procedure was explained. The PSG room was standardized for any noise and visual stimulus based on international standards (1). An overnight PSG (SOMNOscreen plus®, Somnomedics, Randersacker, Germany) was performed for each participant. PSG recordings were started based on the individual's usual sleep habits, and each patient was recorded for a minimum of 7 h.

Polysomnography

The PSG recording and scoring of sleep stages and respiratory events were performed by a sleep physician employing the American Academy of Sleep Medicine (AASM) guidelines (19). Measurement of PSG was based on the AASM guidelines according to the standard techniques, with monitoring of the electroencephalogram using frontal, central and occipital leads referenced to the mastoids (C3M2, F3M2, O1M2, C4M1, F4M1, and O2M1 derivations) according to the 10–20 system, electro-oculogram (EOG), electromyogram (EMG), flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort (induction plethysmography), oximetry, and body position. Respiration was monitored with oronasal thermocouples and nasal pressure transducers. Thoracoabdominal movements were monitored using piezoelectric strain gauges. Continuous pulse oximetry was also monitored.

The AASM criteria (1, 45) were applied to calculate the apnea/hypopnea index (AHI). Hypopnea is defined as a partial cessation of breathing; peak signal excursions drop by $\geq$ 30%, compared to the pre-event baseline for at least 10 s; further, compared to the pre-event baseline, oxygen saturation decreases by $\geq$ 3%; or the partial cessation of breathing is associated with an arousal. Apnea is defined as complete cessation of breathing; compared to the pre-event baseline the peak signal excursion drops by $\geq$ 90% for at least 10 s. AHI is calculated as the sum of apnea and hypopnea events per hour of sleep. AHI was used to confirm the clinical diagnosis. Further, based on the global AHI index, participants were classified into non-OSA (AHI $<$5), mild (5$\leq$AHI$<$15), moderate (15$\leq$AHI$<$30), and severe OSA (30$\leq$AHI) groups. Wake index was calculated as the number of awakenings per hour of sleep. Arousal index is considered as the number of notable EEG shift toward a higher frequency for at least 3 s but no more than 15 s during all non-REM (NREM)

stages per hour of sleep. Sleep efficiency (SE) was calculated as a ratio of total sleep time (TST) to time in bed × 100.

EEG Analysis

All PSG data were digitized with a sampling rate of 256 Hz and the resolution of 16 bits, and then converted into the European Data Format (EDF) for further analysis in Matlab. The EEG signals were first band-pass filtered between 0.5 and 35 Hz using a 12th order Chebyshev Type II filter. EMG, ECG, and EOG artifacts were removed from the EEG signals by the independent component analysis (ICA). Thirty minutes of the EEG signals, 15 min from the beginning and 15 min from the end of each whole-night sleep recording were excluded from analysis to avoid unreliable data collected during wakefulness.

Spindle Detection

We used the method proposed by Ferrarelli et al. (46) to detect sleep spindles through bandpass filtering and amplitude thresholding as implemented in Pareto-optimization software (46, 47). With few adjustable parameters, this method provides a good trade-off between performance and computational complexity (47). To differentiate spindles from EEG background activities and artifacts, the algorithm first preprocesses the EEG signal with a filter using the bandpass setting published by Warby et al. (48). The envelope of the rectified filtered signal peaks is then thresholded (p1 and p2) by two lower and upper amplitude thresholds used to identify spindle candidates. In this approach, to consider variations in signal amplitude between channels, thresholds are set relative to mean signal amplitude. A spindle is detected if its peak amplitude exceeds the upper threshold. The beginning and end of the spindle are determined before and after the spindle peak if the amplitude of the time series drops below the lower threshold. Finally, each spindle candidate is examined by the lower and upper duration criteria p3 and p4 sec. In our analysis, we first bandpass filtered the EEG data between 12 and 15 Hz (−3 dB at 12 and 15 Hz). We set the spindle lower (p1) and upper (p2) boundary threshold ratios to two and four times the average amplitude of the EEG signal for each channel, respectively, so as to achieve maximum sensitivity and low false detection rates. We then selected spindle candidates having a duration within [p3 p4], which were set to 0.5 to 3 s, respectively, as recommended in Liu et al. (47). For each channel, we then computed the spindle density (average number of spindles per minute) and average spindle duration (in sec) for N2 and N3. Spindle density in N2 and N3 was calculated as the ratio of the number of sleep spindles to the number of minutes of N2 and N3 separately.

Statistical Analysis

Comparison of sociodemographic (age, sex) and anthropometric dimensions (BMI) between participants without and with mild, moderate, and severe OSAS was made via a series of X^2-tests and ANOVAs. Sleep characteristics and spindle parameters were compared between the four groups via ANOVAs. Eta squared was used to measure effect size. *Post-hoc* Tukey test were performed for multiple comparisons between the four groups. The statistical comparisons were made on a channel-by-channel basis. Pearson's correlations were computed for associations between AHI, spindle density and spindle duration for all electrode sites (F3, F4, C3, C4, O1, O2). All statistical computations were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Windows®.

RESULTS

Sociodemographic and Anthropometric Findings

Table 1 provides the descriptive and inferential statistical indices for age, sex, and BMI, between the four groups. There were no significant differences between groups. Accordingly, age, sex, and BMI were not introduced as possible confounders.

Sleep Dimensions

Table 2 provides the descriptive and inferential statistical indices for all sleep dimensions, including AHI and O_2% saturation, between the four groups.

A series of ANOVAs was performed to compare sleep characteristics between the groups. AHI, TST, SE, N1, and N3 sleep percent, sleep arousal index, wake index, and minimum sleep O_2% saturation differed significantly between the groups. More specifically, SE and N3% was significantly lower in the groups with moderate and severe OSA, compared to the groups with no and mild OSA. N1% was significantly higher in the group with severe OSA, compared to the groups with no, mild and moderate OSA. N1% did not differ between the groups with no, mild and moderate OSA. No statistically significant group differences were observed for N2% and REM%. The arousal index was significantly higher in the group with severe OSA, compared to the groups with no, mild and moderate OSA. Wake index was statistically significantly higher in the groups of moderate and severe OSA, compared to the groups with no and mild OSA.

Spindles Characteristics

Tables 3, **4** and **Figures 1–4** (along with **Supplementary Tables 1–4**) provide the descriptive and inferential statistical indices of spindle-related characteristics between the four groups. Spindle density was compared between the three OSA groups and control separately for N2 and N3. While descriptively spindle density varied as a function of AHI in N2, for all electrode sites there were no statistically significant mean differences between groups (**Table 3**, **Figure 1**, **Supplementary Table 1**).

In N3, spindle density progressively declined from the control group to the group with severe OSAS (**Figure 2**, **Supplementary Table 2**). Differences were statistically significant between control and the groups with moderate and severe OSAS; no statistically significant mean differences were observed between the groups with no and mild OSA. Further, no statistically significant mean differences were observed between the groups with mild, moderate and severe OSA (**Table 3**, **Figure 2**, **Supplementary Table 2**). These patterns of results were observed in all electrode sites; however, the difference was higher for frontal than for occipital sites.

TABLE 1 | Sociodemographic and anthropometric descriptive and inferential statistical indices of healthy controls and individuals with mild, moderate and severe Obstructive Sleep Apnea.

	Groups				Statistics
	Healthy controls	**Mild OSAs**	**Moderate OSAs**	**Severe OSAs**	
N	23	8	8	15	
	n/n	n/n	n/n	n/n	
Sex (male/female)	16/7	5/3	6/2	13/2	X^2 ($N = 54$, df = 3) = 2.04, $p = 0.56$
	M (SD)	M (SD)	M (SD)	M (SD)	
Age (years)	45.17 (10.73)	44.12 (10.75)	49.37 (8.86)	52.26 (7.11)	$F_{(3,51)} = 2.11$, $p = 0.11$
BMI	27.96 (4.96)	28.66 (3.32)	31.25 (3.97)	31.12 (5.04)	$F_{(3,51)} = 1.89$, $p = 0.14$

BMI, Body Mass Index.

TABLE 2 | Descriptive and inferential statistical indices of sleep-disordered breathing and objective sleep-EEG parameters of healthy controls and individuals with mild, moderate and severe Obstructive Sleep Apnea.

	Groups				Statistics
	Healthy controls	**Mild OSAs**	**Moderate OSAs**	**Severe OSAs**	
N	23	8	8	15	$F_{(3,51)}$; partial etM2; *post-hoc* tests
	M (SD)	M (SD)	M (SD)	M (SD)	
AHI	1.55 (0.97)	10.78 (1.63)	23.81 (3.33)	53.28 (15.96)	114.01**; 0.87 (M); HC < MiOSAs, MoOSAs, SeOSAs; MiOSAs < MoOSAs, SeOSAs; MoOSAs < SeOSAS
TST (h)	7.21 (0.29)	6.99 (0.53)	6.30 (0.88)	6.63 (0.94)	4.78**; 0.22 (L); HC = MiOSAs; HC > MoOSAs, SeOSAs; MiOSAs = MoOSAs = SeOSAs
SE	92.92 (3.72)	93.42 (6.67)	80.72 (11.60)	86.11 (7.92)	8.05**, 0.33 (L); HC = MiOSAs; HC > MoOSAs, SeOSAs; MiOSAs > MoOSAs; MiOSAs = SeOSAS; MoOSAs = SeOSAs
N1%	32.16 (13.90)	39.25 (14.01)	41.61 (23.29)	56.59 (17.79)	6.57**,.28 (L); HC < SeOSAs; MiOSAs = MoOSAs = SeOSAs
N2%	22.44 (13.66)	20.13 (13.38)	28.20 (24.01)	20.92 (11.62)	0.50,.03 (S); HC = MiOSAs = MoOSAs = SeOSAs
N3%	30.44 (15.42)	29.61 (19.37)	12.96 (11.63)	9.36 (10.24)	8.35**,.33 (L); HC > MoOSAs, SeOSAs; MiOSAs > SeOSAs; MoOSAs = SeOSAs
REM%	14.70 (15.73)	10.98 (10.92)	16.05 (15.86)	11.80 (10.63)	0.39, 0.02 (S); HC = MiOSAs = MoOSAs = SeOSAs
Arousals index	25.83 (5.29)	25.32 (3.85)	24.23 (4.76)	31.96 (11.20)	3.04*, 0.15 (L); HC = MiOSAs = MoOSAs = SeOSAs
Wake index	2.45 (1.35)	2.50 (3.13)	5.87 (5.22)	4.81 (3.14)	3.92**, 0.19 (L); HC < MoOSAs; MiOSAs = MoOSAs = SeOSAs
Minimum SpO2%	90.30 (1.76)	82.87 (6.46)	75.50 (11.09)	67.33 (12.48)	24.74***, 0.60 (L); HC > MoOSAs, SeOSAs; MiOSAs > SeOSAs; MoOSAS = SeOSAs

*AHI, apnea/hypapnea index; TST, total sleep time (hour); SE, sleep efficiency; N1%, percent of N1 stage; N2%, percent of N2 stage; N3%, percent of N3 stage; REM%, percent of REM stage; OSAS, Obstructive Sleep Apnea Syndrome; *p < 0.05; **p < 0.01; ***p < 0.001; (S), small effect size; (M), medium effect size; (L), large effect size; >, longer than; <, shorter than, =, as long as; HC, healthy controls; MiOSAs, mild Obstructive Sleep Apnea Syndrome; MoOSAs, moderate Obstructive Sleep Apnea Syndrome; SeOSAs, severe Obstructive Sleep Apnea Syndrome.*

Spindle duration was also compared between the groups of no, mild, moderate and severe OSA, and separately for N2 and N3.

Spindle duration differed significantly between the groups with no, mild, moderate and severe OSA in N2, but not in N3.

In N2, for all electrodes except for C3 and O2, there was a statistically significant mean difference in spindle duration between the four groups (**Table 4**, **Figure 3**, **Supplementary Table 3**). Specifically, for frontal electrodes, the Tukey *post-hoc* analysis showed statistically significant differences between the groups with no, mild, moderate and severe OSA. For central electrodes, compared to the group with no, mild and moderate OSA, the group with severe OSA had a significantly shorter spindle duration.

In N3, no significant differences in spindle duration were found between the groups with no, mild, moderate and severe OSA (**Table 4**, **Figure 4**, **Supplementary Table 4**).

Correlations Between AHI and Spindle-Related Dimensions

Table 5, **Figures 5–8** (**Supplementary Material**) provide the correlations between AHI and spindle-related dimensions, separately for the four groups. No significant correlations were found between AHI and spindle density in N2 (**Table 5**, **Figure 5**). Significant negative correlations were found between AHI and spindle density for all electrodes in N3 ($r < -0.54$; $p < 0.01$; **Table 5**, **Figure 6**).

TABLE 3 | Descriptive and inferential statistical indices of spindle density indices between healthy controls, and individuals with mild, moderate, and severe Obstructive Sleep Apnea.

	Groups				Statistics
	Healthy controls	**Mild OSAs**	**Moderate OSAs**	**Severe OSAs**	
N	23	8	8	15	
	M (SD)	M (SD)	M (SD)	M (SD)	$F_{(3,51)}$; partial etM2; *post-hoc* tests
N2 stage					
F3-M2	1.07 (0.15)	0.89 (0.08)	0.83 (0.07)	0.92 (0.14)	9.28**; 0.36 (L); HC > MiOSAs; MoOSAs; SeOSAs; MiOSAs = MoOSAs = SeOSAs;
F4-M1	1.06 (0.16)	0.90 (0.09)	0.86 (0.14)	0.88 (0.13)	7.09**; 0.30 (L); HC = MoOSAs = SeOSAs;
C3-M2	1.09 (0.26)	0.96 (0.14)	0.94 (0.36)	0.88 (0.12)	2.46(*); 0.13 (M): HC = MoOSAs = SeOSAs;
C4-M1	1.03 (0.25)	0.93 (0.14)	0.92 (0.21)	0.84 (0.10)	2.86*; 0.15 (L); HC = MoOSAs = SeOSAs;
O1-M2	0.91 (0.14)	0.83 (0.08)	0.78 (0.11)	0.79 (0.84)	4.28**; 0.20 (L); HC = MoOSAs = SeOSAs;
O2-M1	0.90 (0.13)	0.85 (0.09)	0.82 (0.15)	0.81 (0.11)	1.94; 0.10 (M); HC = MoOSAs = SeOSAs;
N3 stage					
F3-M2	0.99 (0.17)	0.85 (0.06)	0.86 (0.17)	0.90 (0.16)	2.98*; 0.15 (L); HC > MiOSAs; MoOSAs; SeOSAs; MiOSAS > SeOSAs; MoOSAs = SeOSAs
F4-M1	0.97 (0.16)	0.81 (0.07)	0.87 (0.17)	0.89 (0.17)	2.43(*); 0.13 (M); HC > MoOSAs; SeOSAs; MoOSAs = MiOSAS = SeOSAs
C3-M2	1.01 (0.25)	0.87 (0.13)	1.22 (0.96)	0.91 (0.21)	1.32; 0.07 (M); HC < MoOSAs; HC > SeOSAs; MiOSAS = SeOSAs
C4-M1	0.94 (0.20)	0.85 (0.12)	0.90 (0.25)	0.82 (0.13)	1.36; 0.08 (M); HC > MiOSAs; SeOSAs; MiOSAs = MoOSAs = SeOSAs
O1-M2	0.83 (0.09)	0.79 (0.14)	0.91 (0.37)	0.80 (0.13)	0.76; 0.04 (S); HC < MiOSAS; HC > SeOSAs; MiOSAs = MoOSAs = SeOSAs
O2-M1	0.81 (0.08)	0.78 (0.08)	0.76 (0.09)	0.76 (0.11)	1.26; 0.07 (M); HC > MoOSAs; SeOSAs; MiOSAs = MoOSAs = SeOSAs

OSAS, Obstructive Sleep Apnea Syndrome; $^{(*)}p < 0.1$; $^{*}p < 0.05$; $^{**}p < 0.01$; *(S), small effect size; (M), medium effect size; (L), large effect size; >, longer than; <, shorter than, =, as long as; HC, healthy controls; MiOSAs, mild Obstructive Sleep Apnea Syndrome; MoOSAs, moderate Obstructive Sleep Apnea Syndrome; SeOSAs, severe Obstructive Sleep Apnea Syndrome.*

Figure 7 depicts the gradual decline in spindle duration as a function of AHI in N2. This result was replicated for all electrode sites. In N2, spindle duration was negatively correlated with AHI for all electrodes ($r < -0.39$; $p < 0.01$) (**Table 5**). Although no statistically significant differences were found in spindle duration between the groups for any electrode site (**Table 4**), a tendency to spindles with shorter durations was observed with increasing AHI in N3 and for all electrodes (**Figure 8**). The correlation between AHI and spindle duration in N3 was only significant for F3, C4, and O2 electrodes ($r < -0.30$; $p < 0.02$) (**Table 5**).

DISCUSSION

In the present study, sleep spindle density and sleep spindle duration, along with sleep architecture indices, were investigated topographically in N2 and N3 sleep-EEG signals in a sample of individuals with mild, moderate and severe OSAS and in healthy controls. The key findings were as follows: (1) with increasing OSA severity sleep spindle density decreased in N3, but not in N2. (2) no differences in spindle density were observed between individuals with no and mild OSA, and between individuals with moderate and severe OSA. (3) Such differences were found in the frontal, but not in the occipital area. (4) A higher OSA severity was associated with a shorter spindle duration in N2, but not in N3. (5) A higher spindle density was associated with a lower AHI index in N2, but not in N3. (6) Sleep architecture indices did not differ between individuals with no and mild OSA. (7) Sleep efficiency and total sleep time were significantly lower among participants with moderate and severe OSAS than in participants with mild OSAS or no OSAS. The present pattern of results adds to the current literature in an important way, in that we confirmed that in individuals with OSA sleep spindle density and duration vary in a sophisticated fashion, also depending from the sleep stage (N2 vs. N3), the topographical area (frontal area vs. occipital area) and from the AHI index.

The results on sleep architecture and sleep spindles are considered now in turn.

For sleep architecture, N2% and REM% did not significantly differ between participants without and with mild, moderate and severe OSAS. In contrast, N3% was significantly lower in participants with moderate and severe OSAS, compared to participants with no or mild OSAS; further, N1% was significantly higher in participants with severe OSA than in the other three groups. The pattern of results observed in the present study appears to contradict previous results. Swihart et al. (49) stated that OSA did not influence PSG

TABLE 4 | Descriptive and inferential statistical indices of spindle duration between healthy controls, and individuals with mild, moderate and severe Obstructive Sleep Apnea.

	Groups				Statistics
	Healthy controls	**Mild OSAs**	**Moderate OSAs**	**Severe OSAs**	
N	23	8	8	15	
	M (SD)	M (SD)	M (SD)	M (SD)	$F_{(3,51)}$; partial etM2; *post-hoc* tests
N2 stage					
F3-M2	1.07 (0.15)	0.89 (0.08)	0.83 (0.07)	0.92 (0.14)	9.28**; 0.36 (L); HC > MiOSAS, MoOSAs, SeOSAs; MiOSAs = MoOSAs = SeOSAs
F4-M1	1.06 (0.16)	0.90 (0.09)	0.86 (0.14)	0.88 (0.13)	7.09**; 0.30 (L); HC > MiOSAS, MoOSAs, SeOSAs; MiOSAs = MoOSAs = SeOSAs
C3-M2	1.09 (0.26)	0.96 (0.14)	0.94 (0.36)	0.88 (0.12)	2.46(*); 0.13 (M) HC = MiOSAs = MoOSAs = SeOSAs
C4-M1	1.03 (0.25)	0.93 (0.14)	0.92 (0.21)	0.84 (0.10)	2.86*; 0.15 (L); HC > SeOSAs; MiOSAs = MoOSAs = SeOSAs
O1-M2	0.91 (0.14)	0.83 (0.08)	0.78 (0.11)	0.79 (0.84)	4.28**; 0.20 (L): HC > MoOSAs, SeOSAs;
O2-M1	0.90 (0.13)	0.85 (0.09)	0.82 (0.15)	0.81 (0.11)	1.94; 0.10 (M); HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs
N3 stage					
F3-M2	0.99 (0.17)	0.85 (0.06)	0.86 (0.17)	0.90 (0.16)	2.98*; 0.15 (L): HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs
F4-M1	0.97 (0.16)	0.81 (0.07)	0.87 (0.17)	0.89 (0.17)	2.43(*); 0.13 (M); HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs
C3-M2	1.01 (0.25)	0.87 (0.13)	1.22 (0.96)	0.91 (0.21)	1.32; 0.07 (M); HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs
C4-M1	0.94 (0.20)	0.85 (0.12)	0.90 (0.25)	0.82 (0.13)	1.36; 0.08 (M); HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs
O1-M2	0.83 (0.09)	0.79 (0.14)	0.91 (0.37)	0.80 (0.13)	0.76; 0.04 (S); HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs
O2-M1	0.81 (0.08)	0.78 (0.08)	0.76 (0.09)	0.76 (0.11)	1.26; 0.07 (M); HC= SeOSAs; MiOSAs = MoOSAs = SeOSAs

*OSAS, Obstructive Sleep Apnea Syndrome; (*)p < 0.1; *p < 0.05; **p < 0.01; (S), small effect size; (M), medium effect size; (L), large effect size; >, longer than; <, shorter than, =, as long as; HC, healthy controls; MiOSAs, mild Obstructive Sleep Apnea Syndrome; MoOSAs, moderate Obstructive Sleep Apnea Syndrome; SeOSAs, severe Obstructive Sleep Apnea Syndrome.*

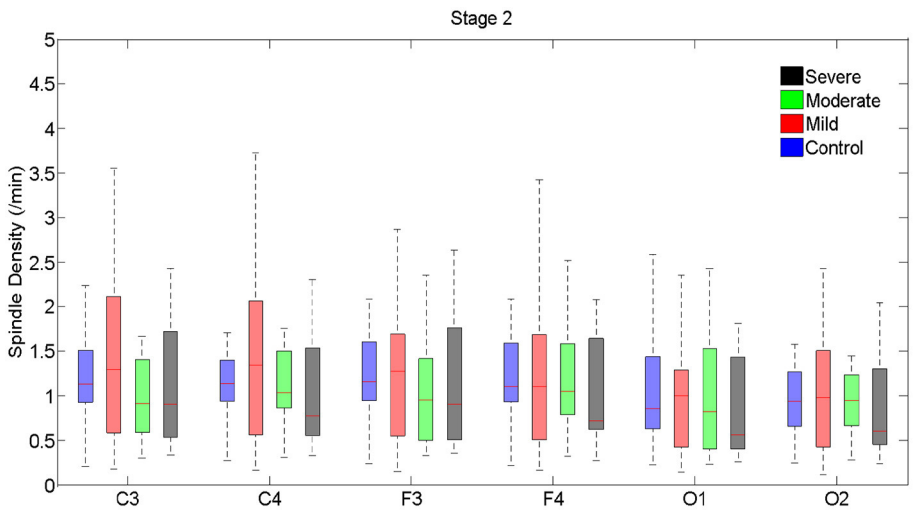

FIGURE 1 | Boxplots displaying the median and interquartile range of sleep spindle density between patients with OSA and normal sleepers in N2 in different measurement sites.

dimensions such as total sleep time or stage percentages. Likewise, Bianchi et al. (50) did not observe significant differences in sleep efficiency between individuals with mild and severe OSAS, while the same authors reported significant differences in percentages of REM, N2 and N3, but not N1 between individuals with mild and severe OSAS. In addition, Andreou et al. (51) reported that N1, N3 and REM decreased, and N2 increased in individuals with OSAS when compared to a control group.

Next, similar to present study, Ratnavadivel et al. (52) reported more N1 and less deep sleep in individuals with OSAS than in healthy controls. Furthermore, Ng and Guan (53) reported that individuals with severe OSAS spent more time in REM-sleep than in deep or light sleep.

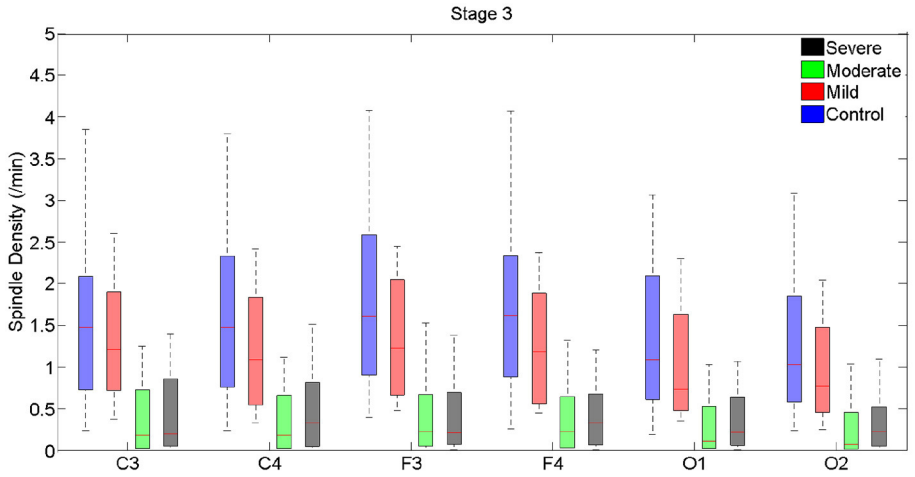

FIGURE 2 | Boxplots displaying the median and interquartile range of sleep spindle density between patients with OSA and normal sleepers in N3 in different measurement sites.

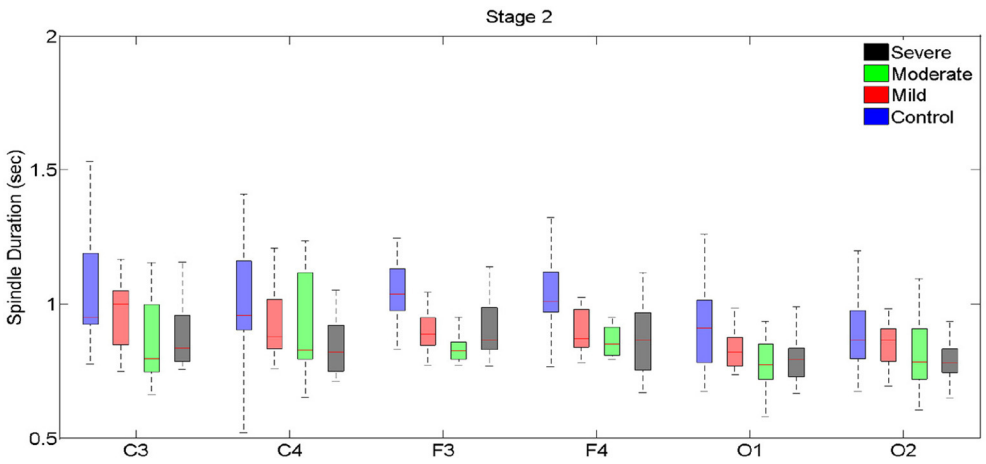

FIGURE 3 | Boxplots displaying the median and interquartile range of sleep spindle duration for patients with OSA and normal sleepers in N2 in different measurement sites.

We also observed that participants with severe OSAS had a significantly higher arousal index than their counterparts with no or with mild or moderate OSAS.

As regards the wake index, this was higher in participants with moderate and severe OSAS than in participants with no or with moderate OSAS. This confirms previous findings (33, 50, 54).

For sleep spindles, these are considered as markers of N2 or nREM sleep microstructures (55, 56). Previous studies have investigated this neurophysiologic phenomenon either only in N2 (22, 37, 40, 57, 58) or in both N2 and N3 stages (58). In the present study, we performed spindle analyses separately for N2 and N3. More specifically, we investigated sleep spindle density and duration in N2 in frontal, central and occipital sites. In addition, for the first time, the duration and density of spindles were investigated separately in N3 stage. Although spindle density did gradually decrease with increasing OSA severity (that is, from no OSA to mild, moderate and severe OSA) the difference between groups was significant in N3, but not in N2. Thus, it appears that, for the first time, differences in sleep spindle signatures were observed in N3 between individuals without and with different degrees of OSAS. Interestingly, a dichotomy in spindle density was found: participants with no or with mild OSAS contrasted clearly with those participants with moderate and severe OSA. Based on this result, we suggest that apnea-hypopnea events below the threshold of 15 events/h may not disrupt normal sleep spindle activity. Or to put it the other way around: While mild OSA does not appear to disrupt the neurophysiological course of spindle density, moderate to severe OSAS does have a negative impact on spindle density.

Next, in N3, spindle density gradually decreased from frontal to occipital electrodes among all participants, and group differences also declined from the frontal to occipital area. To

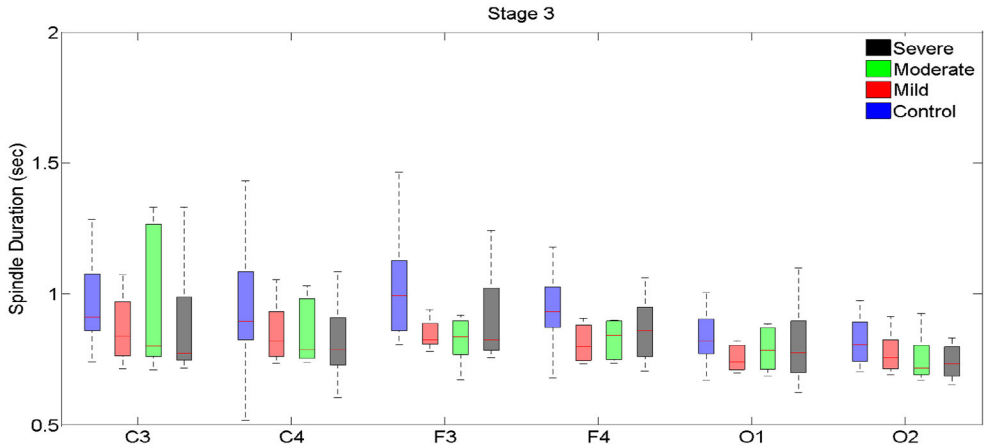

FIGURE 4 | Boxplots displaying the median and interquartile range of sleep spindle duration for patients with OSA and normal sleepers in t N3 in different measurement sites.

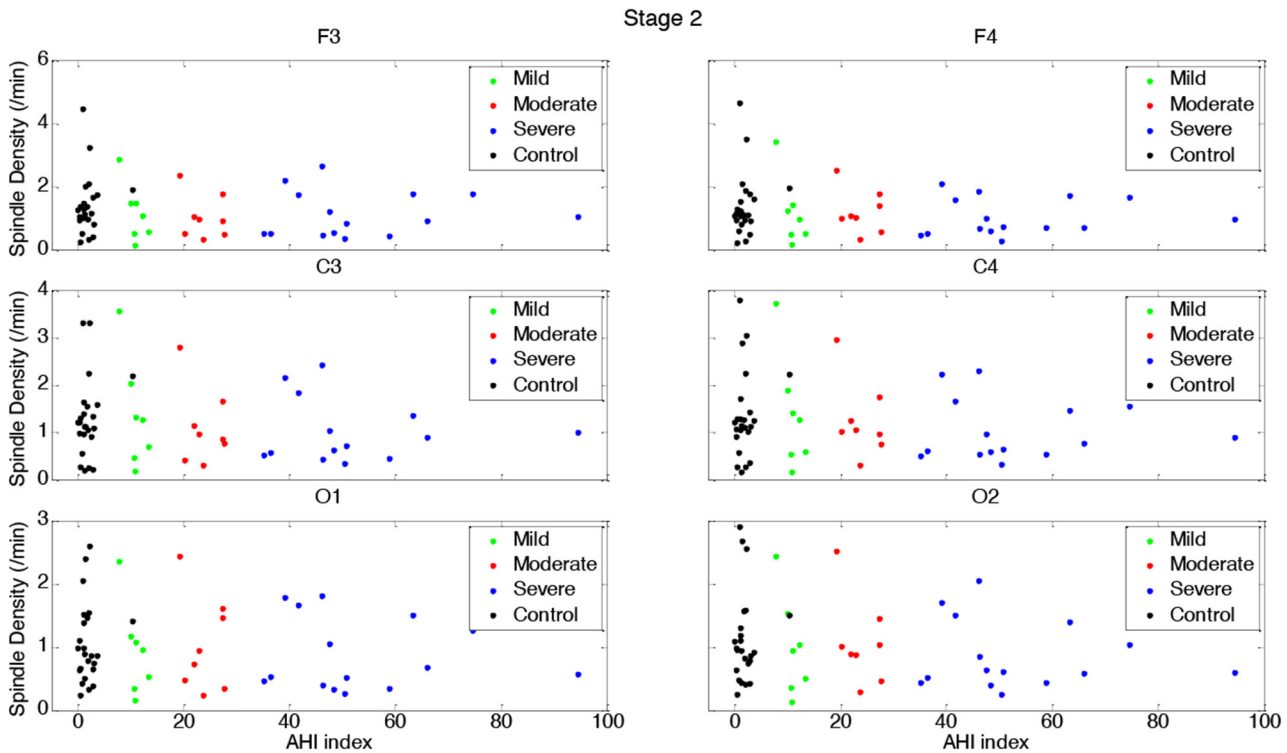

FIGURE 5 | Spindle density distribution vs. AHI in N2 for each group.

put it another way: Spindle density differences between the four groups were more pronounced in the frontal area than in the occipital area. To summarize, we believe that the progressive decline in spindle density with increasing OSAS severity reflects its disruptive effect on the synchronization of the spindle pattern generator in N3 stage.

As in the present study, Schonwald et al. (22) found no significant differences in spindle density between individuals with mild or moderate OSAS and healthy controls in the N2 stage. However, the present study expands upon their results as we investigated spindle density indices in both N2 and N3. Himannen et al. (37) found no significant differences between individuals with and without OSAS in visually detected bi-hemispheric synchronous spindle density during NREM sleep. However, they collapsed N2 and N3 in their analysis while in the present study we analyzed N2 and N3 separately.

TABLE 5 | Correlation coefficients between apnea/hypopnea indices (AHI) and sleep spindle density and duration, separately for different electrodes for the whole sample.

	Correlation coefficient	*p*
Density N2 stage		
F3-A2	−0.11	0.40
F4-A1	−0.13	0.32
C3-A2	−0.11	0.42
C4-A1	−0.13	0.33
O1-A2	−0.12	0.37
O2-A1	−0.18	0.19
Density N3 stage		
F3-A2	−0.61	<0.01
F4-A1	−0.60	<0.01
C3-A2	−0.57	<0.01
C4-A1	−0.56	<0.01
O1-A2	−0.54	<0.01
O2-A1	−0.54	<0.01
Duration N2 stage		
F3-A2	−0.48	<0.01
F4-A1	−0.47	<0.01
C3-A2	−0.41	<0.01
C4-A1	−0.44	<0.01
O1-A2	−0.42	<0.01
O2-A1	−0.39	<0.01
Duration N3 stage		
F3-A2	−0.34	0.01
F4-A1	−0.23	0.08
C3-A2	−0.23	0.09
C4-A1	−0.30	0.02
O1-A2	−0.15	0.27
O2-A1	−0.38	<0.01

Similarly, Huupponen et al. (59) reported no significant differences between individuals with and without OSAS in the total number of spindles. These authors employed an automatic spindle detector and analyzed the whole night sleep-EEG regardless of sleep stages. These differences might explain why the present results did not match those of Huupponen et al. (59).

Ondze et al. (33) found a lower spindle density during NREM sleep (both N2 and N3) in individuals with mild SDB than in healthy controls, but they found no significant differences between individuals with and without OSAS in REM spindle density.

Interestingly, Madaeva et al. (40) reported a higher number of spindles and higher spindle density during N2 in overweight adolescents with OSAS than in either overweight or normal weight healthy controls. As in the present study, Madaeva et al. (40) used an automatic software method to detect sleep spindles. As mentioned, previous studies of adults have investigated spindle density either solely in N2 (40), or for the whole sleep (59), or in NREM sleep (33), while no other study has, as in the present case, focused specifically on N3. One study of children examined spindle density separately in N2 and N3 (39) but its findings are the reverse of our own.

As regards spindle duration, this differed significantly between groups in N2 (except for C3 and O2 electrodes) but not in N3. We also note that only a few studies have investigated spindle duration in individuals with OSAS. In contrast to the present results, Schonwald et al. (22) did not observe significant differences in the spindle duration in N2 when comparing individuals with mild and moderate OSAS to healthy controls. Similarly, Madaeva et al. (40) reported no significant differences in spindle duration during N2 between overweight adolescent individuals with OSAS and either overweight or normal weight healthy controls.

Next, we also found significant associations between a higher spindle density and a lower AHI in N3, and between a longer spindle duration and a lower AHI in N2. Similarly, Li et al. (36) reported a significant association between a higher number of sleep spindle in N3 and a lower AHI, independently of sleep efficiency. Likewise, Madaeva et al. (40) reported significant associations between more favorable spindle characteristics and a lower AHI, a higher SaO2, and a lower total arousal index.

To summarize, our results show that OSAS produces a significant disruption of spindle density in N3, but not in N2. Unlike density, spindle duration was lower in moderate/severe OSAS during N2. It seems that, in individuals with moderate and severe OSAS, first the duration of spindles decreases during N2, and then the numbers of the spindles decrease in N3. The gradual decline in spindle duration in N2 may have led to reduction to such a level as to be too short to identify spindle activities. A similar process might have occurred for spindle density decline in N3. Our results also revealed that in contrast to moderate and severe OSAS, the mild condition of the disorder does not have a significant adverse effect on sleep spindle characteristics.

Some researchers have excluded apnea and hypopnea events so as to minimize any potential confounding effect caused by alpha activity in the automatic detection of slow spindles (22, 57). But respiratory events such as apnea have been shown to affect EEG frequency (29, 60). Dingli et al. (29) reported a significant elevation in sigma power among individuals with OSAS following respiratory events associated with an arousal (vs. without an arousal) during NREM and total sleep. Although they linked this finding to arousal-induced EMG activity and its effect on EEG, increased sigma power might reflect the hypothesized sleep maintenance function of spindle activity (34). Apnea and hypopnea events were not filtered out from the analysis in the present study because of the critical impact of these events on EEG activity.

Overall, the present controversy in the scientific literature as regards the occurrence (or otherwise) of sleep spindles in individuals with OSAS may be due to methodological issues, the use of different methodologies for spindle detection, choice of different sleep stages for analysis, and investigation of different characteristics such as sigma band power, total number of spindles, spindle density and duration.

Despite the novelty of the results, the following limitations should be taken into consideration. First, while we divided the OSA sample into subgroups on the basis of OSA severity, the

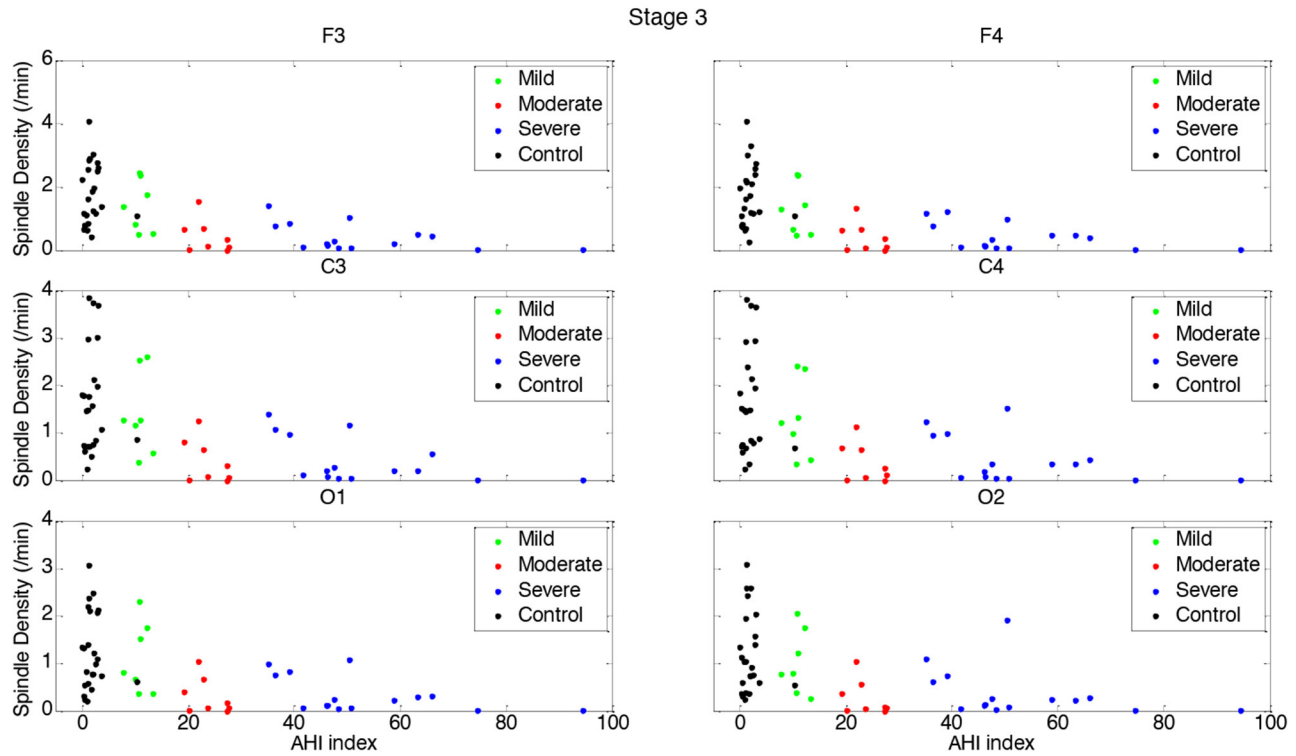

FIGURE 6 | Spindle density distribution vs. AHI in N3 for each group.

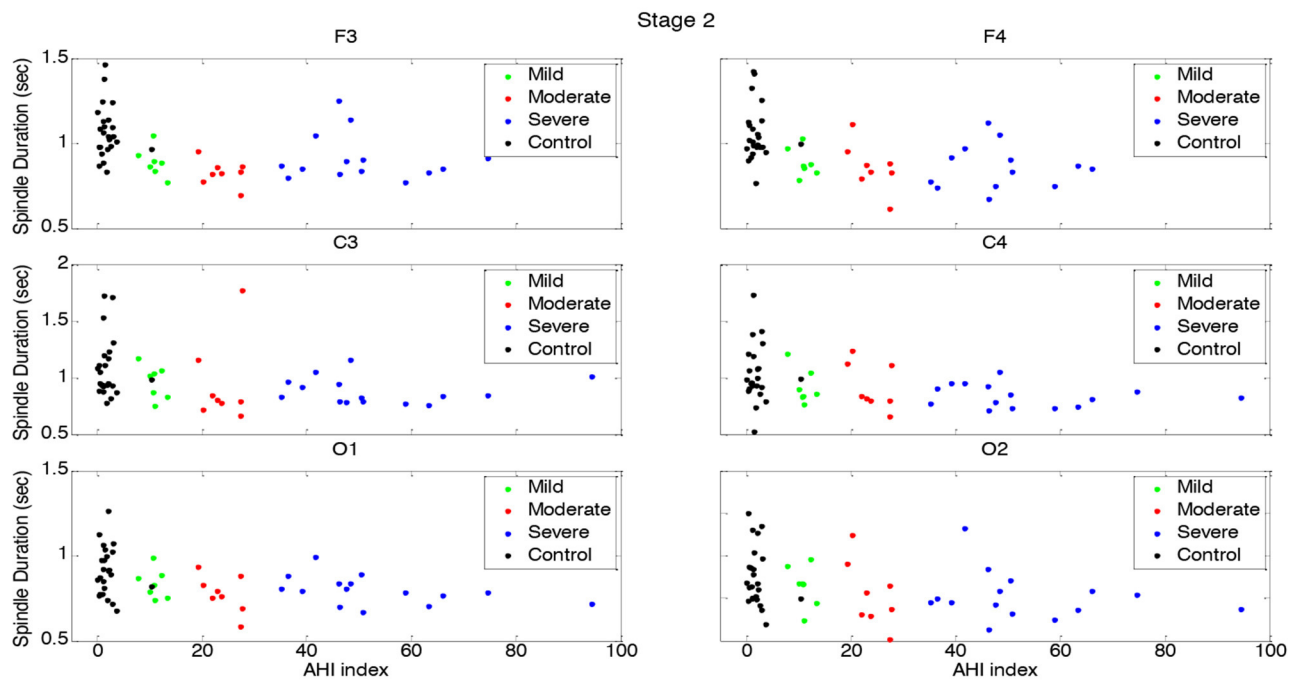

FIGURE 7 | Spindle duration distribution vs. AHI in N2 for each group.

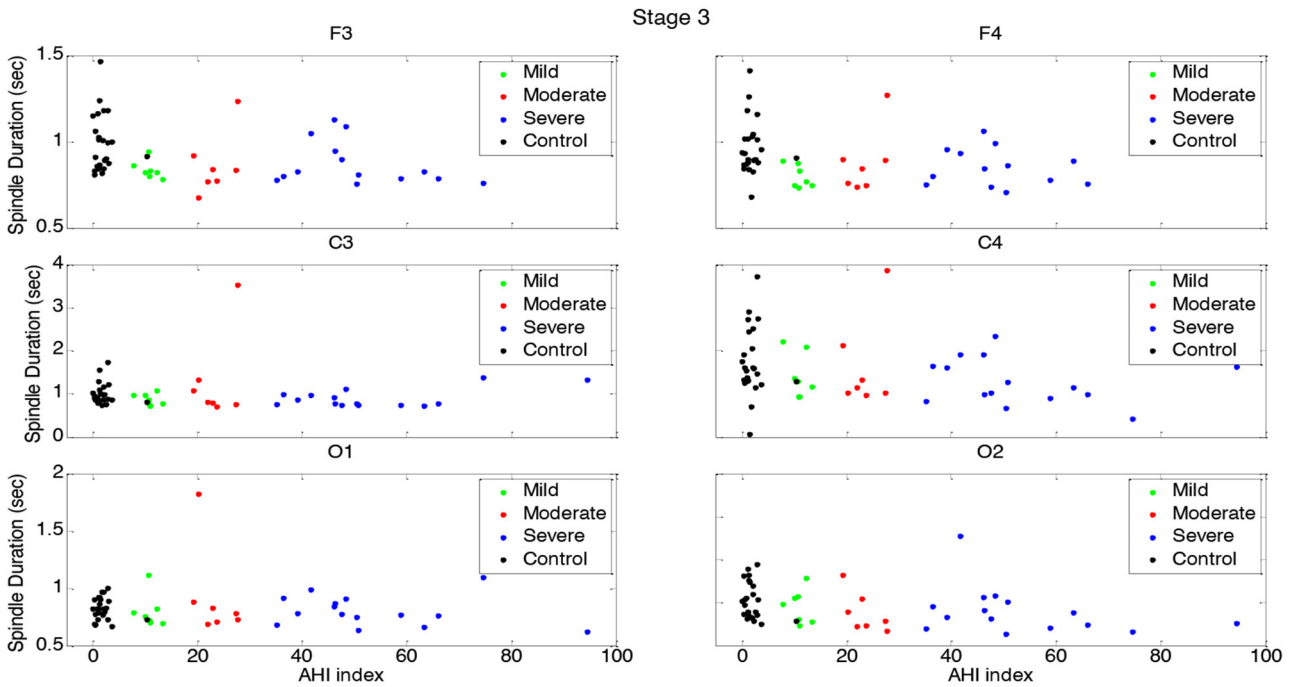

FIGURE 8 | Spindle duration vs. AHI in N3 for each group.

resulting small sample sizes might have precluded more fine-grained patterns of results. However, the statistical analyses were also based on effect size calculations, which by definition are not sensitive to sample sizes. Second, we made a whole night EEG analysis, and dynamic changes in spindles and densities across the night may have influenced the results. Or simply put, no time-of-night effects were tested, although these were found to be relevant in earlier reports. Third, we didn't perform any analysis on fast vs. slow spindle characteristics. Fourth, we used a relatively simple and efficient spindle detection method providing a good trade-off between performance and computational complexity with few adjustable parameters. There are, however, more efficient tools with higher complexities, which require parameter optimization using multi-objective evolutionary algorithms as suggested in Chokroverty et al. (48). Next, the temporal evolution of slow and fast spindles in terms of amplitude and frequency and their density over the course of a full night's sleep can provide valuable information about the influence of OSA severity on spindle frequency distribution. These limitations highlight an important focus for future investigations. In addition, no control for multiple comparisons was considered. Further, there is evidence that a shortened sleep spindle duration was associated with dementia (28). In this line, a lower sleep spindle activity was associated with a lower cognitive performance (11–14, 21–24), and social competences in primary school children (25–27). It follows that future studies on sleep spindle indices in individuals with OSA should assess also participants' cognitive processes. Next, longitudinal studies might investigate, if among individuals with OSA sleep spindle indices are related to a lower quality of life (5), an increased risk of systemic comorbidities such as cardiovascular diseases, hypertension, and metabolic syndrome (6–8). Last, the quality of the data did not allow to test the hypothesis, if group differences in N3 sleep, but not so much in N2 sleep, was the result of an increasing frequency of apnea events during the course of the deepening of sleep.

CONCLUSION

Although sleep spindles are primarily considered as characteristics of the N2 stage, our results showed that an increasing OSA severity was associated with a significant disruption of spindle density in N3, but not in N2. We recommend investigation of spindle characteristics in both N2 and N3 in future studies. Unlike density, spindle duration was lower in individuals with moderate and severe OSAS during the N2 stage. Our results also revealed that, in contrast to moderate and severe OSAS, the mild condition of the disorder does not have a significant adverse effect on sleep spindle characteristics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Kermanshah University of Medical Sciences, Kermanshah, Iran. The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by Kermanshah University of Medical Sciences (grant number: 95602).

ACKNOWLEDGMENTS

Authors acknowledge the staff of SDRC (Kermanshah, Iran) for their assistances. We also thank the Clinical Research Development Center of Imam Reza Hospital in Kermanshah for their statistical advice. Finally, we thank Nick Emler (University of Surrey, Surrey UK) for proofreading the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.598632/full#supplementary-material

REFERENCES

1. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders (Third edition ed.)*. Darien, IL: American Academy of Sleep Medicine. (2014).
2. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* (2013) 177:1006–14. doi: 10.1093/aje/kws342
3. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respiratory Med.* (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
4. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA. Obstructive sleep apnea syndrome in the São Paulo Epidemiologic Sleep Study. *Sleep Med.* (2010) 11:441–6. doi: 10.1016/j.sleep.2009.10.005
5. Khazaie H, Najafi F, Rezaie L, Tahmasian M, Sepehry AA, Herth FJ. Prevalence of symptoms and risk of obstructive sleep apnea syndrome in the general population. *Arch Iran Med.* (2011) 14:335–8. doi: 10.1016/j.sleep.2013.11.390
6. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Prog Cardiovasc Dis.* (2009) 51:285–93. doi: 10.1016/j.pcad.2008.08.001
7. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. *Chest.* (2015) 147:266–74. doi: 10.1378/chest.14-0500
8. Pedrosa RP, Barros IM, Drager LF, Bittencourt MS, Medeiros AKL, Carvalho LL, et al. OSA is common and independently associated with hypertension and increased arterial stiffness in consecutive perimenopausal women. *Chest.* (2014) 146:66–72. doi: 10.1378/chest.14-0097
9. Davies R. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. *Eur Respiratory J.* (1990) 3:509–14.
10. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Critical Care Med.* (2005) 172:1590–5. doi: 10.1164/rccm.200504-637OC
11. Djonlagic I, Guo M, Matteis P, Carusona A, Stickgold R, Malhotra A. Untreated sleep-disordered breathing: links to aging-related decline in sleep-dependent memory consolidation. *PLoS ONE.* (2014) 9:e85918. doi: 10.1371/journal.pone.0085918
12. Liguori C, Mercuri NB, Izzi F, Romigi A, Cordella A, Sancesario G, et al. Obstructive sleep apnea is associated with early but possibly modifiable Alzheimer's disease biomarkers changes. *Sleep*. (2017) 40. doi: 10.1093/sleep/zsx011
13. Daulatzai MA. Evidence of neurodegeneration in obstructive sleep apnea: relationship between obstructive sleep apnea and cognitive dysfunction in the elderly. *J Neurosci Res.* (2015) 93:1778–94. doi: 10.1002/jnr.23634
14. Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. *Am J Respir Crit Care Med.* (2018) 197:933–43. doi: 10.1164/rccm.201704-0704OC
15. Astori S, Wimmer RD, Luthi A. Manipulating sleep spindles–expanding views on sleep, memory, and disease. *Trends Neurosci.* (2013) 36:738–48. doi: 10.1016/j.tins.2013.10.001
16. Genzel L, Kroes MC, Dresler M, Battaglia FP. Light sleep versus slow wave sleep in memory consolidation: a question of global versus local processes? *Trends Neurosci*. (2014) 37:10–9. doi: 10.1016/j.tins.2013.10.002
17. Rasch BR, Born J. About sleep's role in memory. *Physiol Rev*. (2013) 93:681–766. doi: 10.1152/physrev.00032.2012
18. Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger MM, Hirshkowitz M, et al. The visual scoring of sleep in adults. *J Clin Sleep Med.* (2007) 3:121–31. doi: 10.5664/jcsm.26814
19. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* (Vol. 1). Westchester, IL: American Academy of Sleep Medicine. (2007).
20. Piantoni G, Poil SS, Linkenkaer-Hansen K, Verweij IM, Ramautar JR, Van Someren EJ, et al. Individual differences in white matter diffusion affect sleep oscillations. *J Neurosci.* (2013) 33:227–33. doi: 10.1523/JNEUROSCI.2030-12.2013
21. De Gennaro L, Ferrara M, Vecchio F, Curcio G, Bertini M. An electroencephalographic fingerprint of human sleep. *Neuroimage*. (2005) 26:114–22. doi: 10.1016/j.neuroimage.2005.01.020
22. Schonwald SV, Carvalho DZ, de Santa-Helena EL, Lemke N, Gerhardt GJ. Topography-specific spindle frequency changes in obstructive sleep apnea. *BMC Neurosci.* (2012) 13:89. doi: 10.1186/1471-2202-13-89
23. Lustenberger C, Wehrle F, Tushaus L, Achermann P, Huber R. The Multidimensional Aspects of Sleep Spindles and Their Relationship to Word-Pair Memory Consolidation. *Sleep.* (2015) 38:1093–103. doi: 10.5665/sleep.4820
24. Urakami Y, Ioannides AA, Kostopoulos GK. *Sleep Spindles—as a Biomarker of Brain Function and Plasticity* (Vol. 4): chapter (2012). doi: 10.5772/48427
25. Mikoteit T, Brand S, Beck J, Perren S, von Wyl A, von Klitzing K, et al. Visually detected NREM Stage 2 sleep spindles in kindergarten children are associated with stress challenge and coping strategies. *World J Biol Psychiatry.* (2012) 13:259–68. doi: 10.3109/15622975.2011.562241
26. Mikoteit T, Brand S, Beck J, Perren S, Von Wyl A, Von Klitzing K, et al. Visually detected NREM Stage 2 sleep spindles in kindergarten children are associated with current and future emotional and behavioural characteristics. *J Sleep Res.* (2013) 22:129–36. doi: 10.1111/j.1365-2869.2012.01058.x
27. Mikoteit T, Brand S, Perren S, von Wyl A, von Klitzing K, Kurath J, et al. Visually detected non-rapid eye movement stage 2 sleep spindle density at age five years predicted prosocial behavior positively and hyperactivity scores negatively at age nine years. *Sleep Med.* (2018) 48:101–6. doi: 10.1016/j.sleep.2018.03.028
28. Ktonas P, Golemati S, Xanthopoulos P, Sakkalis V, Ortigueira MD, Tsekou H, et al. "Potential dementia biomarkers based on the time-varying microstructure of sleep EEG spindles," in *Paper presented at the 2007 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Lyon (2007). doi: 10.1109/IEMBS.2007.4352827

29. Dingli K, Assimakopoulos T, Fietze I, Witt C, Wraith PK, Douglas NJ. Electroencephalographic spectral analysis: detection of cortical activity changes in sleep apnoea patients. *Eur Respir J.* (2002) 20:1246–53. doi: 10.1183/09031936.02.00288202
30. Abdullah H, Maddage NC, Cosic I, Cvetkovic D. Cross-correlation of EEG frequency bands and heart rate variability for sleep apnoea classification. *Med Biol Eng Comp.* (2010) 48:1261–9. doi: 10.1007/s11517-010-0696-9
31. D'Rozario AL, Cross NE, Vakulin A, Bartlett DJ, Wong KKH, Wang D, et al. Quantitative electroencephalogram measures in adult obstructive sleep apnea - potential biomarkers of neurobehavioural functioning. *Sleep Med Rev.* (2017) 36:29–42. doi: 10.1016/j.smrv.2016.10.003
32. Jones SG, Riedner BA, Smith RF, Ferrarelli F, Tononi G, Davidson RJ, et al. Regional reductions in sleep electroencephalography power in obstructive sleep apnea: a high-density EEG study. *Sleep.* (2014) 37:399–407. doi: 10.5665/sleep.3424
33. Ondze B, Espa F, Dauvilliers Y, Billiard M, Besset A. Sleep architecture, slow wave activity and sleep spindles in mild sleep disordered breathing. *Clin Neurophysiol.* (2003) 114:867–74. doi: 10.1016/S1388-2457(02)00389-9
34. Weiner OM, Dang-Vu TT. Spindle oscillations in sleep disorders: a systematic review. *Neural Plast.* (2016) 2016:7328725. doi: 10.1155/2016/7328725
35. Guilleminault C, Do Kim Y, Chowdhuri S, Horita M, Ohayon M, Kushida C. Sleep and daytime sleepiness in upper airway resistance syndrome compared to obstructive sleep apnoea syndrome. *Eur Respiratory J.* (2001) 17:838–47. doi: 10.1183/09031936.01.17508380
36. Li W, Duan Y, Yan J, Gao H, Li X. Association between loss of sleep-specific waves and age, sleep efficiency, body mass index, and apnea-hypopnea index in human N3 sleep. *Aging Dis.* (2020) 11:73–81. doi: 10.14336/AD.2019.0420
37. Himanen SL, Virkkala J, Huupponen E, Hasan J. Spindle frequency remains slow in sleep apnea patients throughout the night. *Sleep Med.* (2003) 4:361–6. doi: 10.1016/S1389-9457(03)00155-2
38. Appleton SL, Vakulin A, D'Rozario A, Vincent AD, Teare A, Martin SA, et al. Quantitative electroencephalography measures in rapid eye movement and nonrapid eye movement sleep are associated with apnea–hypopnea index and nocturnal hypoxemia in men. *Sleep*. (2019) 42:zsz092. doi: 10.1093/sleep/zsz092
39. Brockmann PE, Damiani F, Pincheira E, Daiber F, Ruiz S, Aboitiz F, et al. Sleep spindle activity in children with obstructive sleep apnea as a marker of neurocognitive performance: a pilot study. *Eur J Paediatr Neurol.* (2018) 22:434–9. doi: 10.1016/j.ejpn.2018.02.003
40. Madaeva I, Berdina O, Rychkova L, Bugun O. Sleep spindle characteristics in overweight adolescents with obstructive sleep apnea syndrome. *Sleep Biol Rhythms.* (2017) 15:251–7. doi: 10.1007/s41105-017-0104-z
41. Chokroverty S, Bhat S, Donnelly D, Gupta D, Rubinstein M, DeBari VA. Sleep spindle density increases after continuous positive airway pressure titration in severe obstructive sleep apnea: a preliminary study. *Sleep Med.* (2015) 16:1029. doi: 10.1016/j.sleep.2015.05.004
42. Saunamaki T, Huupponen E, Loponen J, Himanen SL. CPAP treatment partly normalizes sleep spindle features in obstructive sleep apnea. *Sleep Disord.* (2017) 2017:2962479. doi: 10.1155/2017/2962479
43. Yetkin O, Aydogan D. Effect of CPAP on sleep spindles in patients with OSA. *Respir Physiol Neurobiol.* (2018) 247:71–3. doi: 10.1016/j.resp.2017.09.008
44. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. (2013) 310:2191–4. doi: 10.1001/jama.2013.281053
45. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* (2017) 13:479–504. doi: 10.5664/jcsm.6506
46. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry.* (2007) 164:483–92. doi: 10.1176/ajp.2007.164.3.483
47. Liu MY, Huang A, Huang NE. Evaluating and improving automatic sleep spindle detection by using multi-objective evolutionary algorithms. *Front Hum Neurosci.* (2017) 11:261. doi: 10.3389/fnhum.2017.00261
48. Warby SC, Wendt SL, Welinder P, Munk EG, Carrillo O, Sorensen HB, et al. Sleep-spindle detection: crowdsourcing and evaluating performance of experts, non-experts and automated methods. *Nat Methods*. (2014) 11:385–92. doi: 10.1038/nmeth.2855
49. Swihart BJ, Caffo B, Bandeen-Roche K, Punjabi NM. Characterizing sleep structure using the hypnogram. *J Clin Sleep Med.* (2008) 4:349–55. doi: 10.5664/jcsm.27236
50. Bianchi MT, Cash SS, Mietus J, Peng C-K, Thomas R. Obstructive sleep apnea alters sleep stage transition dynamics. *PLoS ONE.* (2010) 5:e11356. doi: 10.1371/journal.pone.0011356
51. Andreou G, Vlachos F, Makanikas K. Effects of chronic obstructive pulmonary disease and obstructive sleep apnea on cognitive functions: evidence for a common nature. *Sleep Disord.* (2014) 2014:768210. doi: 10.1155/2014/768210
52. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med.* (2009) 5:519–24. doi: 10.5664/jcsm.27651
53. Ng AK, Guan C. Impact of obstructive sleep apnea on sleep-wake stage ratio. *Conf Proc IEEE Eng Med Biol Soc.* (2012) 2012:4660–3. doi: 10.1109/EMBC.2012.6347006
54. Malhotra A, Jordan A. The importance of arousal in obstructive sleep apnea—updates from the American Thoracic Society 2016. *J Thoracic Dis.* (2016) 8:S542–S544. doi: 10.21037/jtd.2016.06.81
55. Fogel SM, Smith CT. The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neurosci Biobehav Rev.* (2011) 35:1154–65. doi: 10.1016/j.neubiorev.2010.12.003
56. Schabus M, Dang-Vu TT, Albouy G, Balteau E, Boly M, Carrier J, et al. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. *Proc Natl Acad Sci USA*. (2007) 104:13164–9. doi: 10.1073/pnas.0703084104
57. Carvalho DZ, Gerhardt GJ, Dellagustin G, de Santa-Helena EL, Lemke N, Segal AZ, et al. Loss of sleep spindle frequency deceleration in obstructive sleep apnea. *Clin Neurophysiol.* (2014) 125:306–12. doi: 10.1016/j.clinph.2013.07.005
58. Lee YJ, Kim JW, Lee YJ, Jeong DU. Sleep EEG characteristics in young and elderly patients with obstructive sleep apnea syndrome. *Psychiatry Investig.* (2016) 13:217–21. doi: 10.4306/pi.2016.13.2.217
59. Huupponen E, Himanen S-L, Hasan J, Värri A. Automatic analysis of electroencephalogram sleep spindle frequency throughout the night. *Med Biol Eng Comp.* (2003) 41:727–32. doi: 10.1007/BF02349981
60. Chervin RD, Burns JW, Ruzicka DL. Electroencephalographic changes during respiratory cycles predict sleepiness in sleep apnea. *Am J Respir Critical Care Med.* (2005) 171:652–8. doi: 10.1164/rccm.200408-1056OC

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 06 April 2021
doi: 10.3389/fneur.2021.620799

Prevalence, Risk Factors, and Comorbidities of Obstructive Sleep Apnea Risk Among a Working Population in Kuwait: A Cross-Sectional Study

Husain Al-Qattan[1†], Hamad Al-Omairah[2†], Khaled Al-Hashash[3], Fahad Al-Mutairi[4], Mohammad Al-Mutairat[5], Mohammad Al-Ajmi[6], Anwar Mohammad[7], Abdulmohsen Alterki[8,9] and Ali H. Ziyab[10]*

[1] Department of Nuclear Medicine, Adan Hospital, Ministry of Health, Kuwait City, Kuwait, [2] Department of Ophthalmology, Al-Bahar Eye Center, Ministry of Health, Kuwait City, Kuwait, [3] Department of Obstructive and Gynecology, Maternity Hospital, Ministry of Health, Kuwait City, Kuwait, [4] Department of Internal Medicine, Farwaniya Hospital, Ministry of Health, Kuwait City, Kuwait, [5] Al-Rawda Health Center, Ministry of Health, Kuwait City, Kuwait, [6] Al-Shuhada Health Center, Ministry of Health, Kuwait City, Kuwait, [7] Department of Biochemistry and Molecular Biology, Dasman Diabetes Institute, Kuwait City, Kuwait, [8] Department of Otolaryngology, Head, and Neck Surgery, Zain and Al-Sabah Hospitals, Ministry of Health, Kuwait City, Kuwait, [9] Medical Division, Dasman Diabetes Institute, Kuwait City, Kuwait, [10] Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait

OPEN ACCESS

Edited by:
Luigi De Gennaro,
Sapienza University of Rome, Italy

Reviewed by:
Abdulghani Sankari,
Wayne State University, United States
Mohammed Al-Abri,
Sultan Qaboos University, Oman

***Correspondence:**
Ali H. Ziyab
ali.ziyab@ku.edu.kw

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Neurology

Received: 26 October 2020
Accepted: 10 March 2021
Published: 06 April 2021

Citation:
Al-Qattan H, Al-Omairah H, Al-Hashash K, Al-Mutairi F, Al-Mutairat M, Al-Ajmi M, Mohammad A, Alterki A and Ziyab AH (2021) Prevalence, Risk Factors, and Comorbidities of Obstructive Sleep Apnea Risk Among a Working Population in Kuwait: A Cross-Sectional Study. Front. Neurol. 12:620799. doi: 10.3389/fneur.2021.620799

Background: Obstructive sleep apnea (OSA) affects a considerable proportion of adults globally and is associated with elevated morbidity and mortality. Given the lack of epidemiologic data on the burden of OSA in Kuwait, this study sought to estimate its prevalence, associated risk factors, and comorbid conditions among a working population in Kuwait.

Methods: This was a cross-sectional study of a sample of working adults ($n = 651$) from public institutions in Kuwait. High/low risk for OSA was ascertained according to the Berlin Questionnaire criteria. Participants self-reported their coexisting health conditions. Associations were assessed using Poisson regression with robust variance estimation; adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) were estimated.

Results: Overall, 20.0% (130/651) of participants were classified as being at high risk for OSA, with more male than female subjects being at high risk (24.0% [56/233] vs. 17.7% [74/418], $P = 0.053$), though this difference did not gain statistical significance. Moreover, a high risk for OSA was more common among older and obese subjects. Factors associated with increased prevalence of a high risk for OSA included current smoking status (aPR = 1.58, 95% CI: 1.02–2.06), longer hours spent watching television (1.76, 1.10–2.81), and lower self-perceived physical health (2.11, 1.15–3.87). However, decreasing trends in the prevalence of high risk for OSA were observed with frequent engagement in vigorous physical activity and longer nightly sleep duration. Compared to those at a low risk for OSA, the subjects at high risk for OSA were more likely to have insomnia disorder (2.83, 1.81–4.41), diabetes (1.94, 1.15–3.27), hypertension (3.00, 1.75–5.16), and depression (4.47, 1.80–11.08).

Conclusion: This study estimated that 1/5 of working adults in Kuwait were at high risk for OSA, and the prevalence varied according to personal characteristics and lifestyle factors. Also, a high risk for OSA classification was associated with multiple comorbid health conditions.

Keywords: obstructive sleep apnea, risk factors, comorbidities, prevalence, Kuwait, adults

INTRODUCTION

Sleep disorders are broadly defined as medical disorders affecting sleep quality and quantity that are associated with increased morbidity and mortality, reduced quality-of-life, and impaired physical and mental functioning (1, 2). Signs and symptoms of sleep disorders may include excessive daytime sleepiness, irregular breathing or increased movement during sleep, and difficulty falling asleep and maintaining sleep (1, 3). Obstructive sleep apnea (OSA) is a common and major sleep disorder that is characterized by frequent and repeated episodes of partial (hypopnea) or complete (apnea) collapses of the upper airway during sleep that interrupt normal breathing (4). The most common cause that leads to arousal from sleep and/or oxygen desaturation during OSA events is oropharyngeal collapse at the back of the throat (4, 5), which results from a combination of anatomical factors that predispose the upper airway to collapse during inspiration and an insufficiency of neuromuscular compensation to maintain airway patency during sleep (6, 7). Snoring is the most common symptom experienced during sleep that is associated with OSA, whereas daytime symptoms include fatigue, excessive sleepiness, morning headaches, and poor concentration (5, 7, 8). Collectively, if left untreated, OSA can have serious and life-shortening consequences.

Worldwide, OSA remains a major source of morbidity and mortality, although estimates of its prevalence vary depending on personal characteristics (e.g., age, sex, obesity, race/ethnicity), as well as the methods and definitions used to ascertain OSA status (9, 10). Based on polysomnography assessment, prevalence estimates of mild OSA (apnea-hypopnea index [AHI] $\geq$5 to $<$15) have been shown to range from 9 to 38%, and estimates of the prevalence of moderate-to-severe OSA (AHI $\geq$15) vary from 6 to 17% among adults in the general population (9, 11). In large epidemiologic studies, the use of polysomnography is constrained by cost and logistics; hence, several questionnaires have been developed to identify subjects at a "high risk for OSA" in large population-based studies. These include the Berlin Questionnaire, the STOP questionnaire, the STOP-Bang questionnaire, and the Epworth Sleepiness Scale, with each instrument demonstrating differing accuracy (12–14).

Several unmodifiable and modifiable risk factors have been identified that influence the development of OSA. Unmodifiable risk factors include older age, male sex, race/ethnicity, family history of OSA, menopause in women, and craniofacial abnormalities (5, 15–17). The major modifiable risk factors of OSA include obesity, smoking, and alcohol use (5, 17, 18). Moreover, OSA has been linked with several comorbid conditions, such as stroke, myocardial infarction, hypertension, hyperlipidemia, diabetes, depression, and cognitive impairment (5, 6, 18–21). Thus, OSA affects a considerable proportion of the general population worldwide and is associated with an elevated public health burden, and empirical evidence leading to a better understanding of the burden of OSA is essential to guide prevention strategies. In Kuwait, obesity, a major risk factors for OSA, is highly prevalent and has been estimated to affect 40.3% (men: 36.5%; women: 44.0%) of adults (22). Hence, such an elevated prevalence of obesity may correlate with higher burden of OSA among adults in Kuwait. Given the scarcity of epidemiologic data on the OSA burden in Kuwait, this study sought to estimate the prevalence of those categorized as being at "high risk for OSA" using the Berlin Questionnaire among a working population in Kuwait and to ascertain the associated risk factors and comorbidities.

MATERIALS AND METHODS

Study Setting, Design, and Participants

A population-based cross-sectional study was conducted to estimate the prevalence of being at a high-risk for OSA and to determine the potential associated risk factors and comorbidities among a working population in Kuwait. Study subjects were recruited from governmental/public workplaces (ministries/authorities) across Kuwait to represent working adults. From a comprehensive list of all the ministries and public authorities in Kuwait, seven venues were randomly selected using random digits. Subsequently, permissions were obtained to gain access to the selected venues, and employees (n = 651, aged 21–60 years) at the respective workplaces were enrolled as a convenience sample between December 2014 and January 2015. Hence, available and willing employees at the time of the study were enrolled. The study was approved by the Health Sciences Center Ethics Committee for Student Research at Kuwait University. Written informed consent was obtained from each study participant prior to enrolment. The study was conducted in accordance with the principles and guidelines of the Declaration of Helsinki for medical research involving human subjects.

Study Questionnaires and Variable Definitions

Study participants were asked to complete the study questionnaire, which collected information on demographic characteristics, including height and weight, history of clinical conditions, lifestyle factors, and behavioral habits. In addition, the Berlin Questionnaire was used to ascertain each participant's

OSA risk status (23), and the Insomnia Symptom Questionnaire (ISQ) was used to determine each subject's insomnia status (24). The study questionnaire (including the Berlin Questionnaire and the ISQ) was develop using English language and then translated into Arabic language. The comprehensibility and meaning of the translated questionnaire were pre-tested by 10 Arabic and English speaking subjects, and modifications were made as necessary. The final version of the Arabic questionnaire was back translated to English by an independent bilingual person to ensure neutral and valid translation. The back translated version was highly comparable to the original English language questionnaire. The used Arabic-translated Berlin Questionnaire is provided as an online supplementary material (see **Supplementary Material**).

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m^2). Standard BMI groupings were applied, which included the following: underweight (BMI $<$ 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), obesity class I (BMI 30.0–34.9), and obesity class II/III (BMI $\geq$35) (25). The underweight category was combined with the normal weight category, as only 15 (2.4%) subjects were classified as being underweight. Cigarette smoking was self-reported based on the following three categories: "never smoked," "former smoker" (did not smoke cigarettes in the past 30 days), and "current smoker" (any cigarette smoking in the past 30 days). The frequency in which the subjects engaged in vigorous physical activities was assessed by the following question: "How many times a week do you engage in vigorous physical activity long enough to make you breathe hard?" The duration of television viewing was assessed by the following question: "During a normal week, how many hours a day (24 h) do you watch television?" Each participant's self-perceived physical health was assessed by asking the following question: "How would you rate your physical health?" The possible responses included "excellent," "very good," "good," "fair," and "poor." The average number of daily hours of paid work was reported by each participant. Similarly, the average number of hours of nightly sleep during a regular working week was also reported.

With regard to existing health conditions, participants were asked the following question: "Has a doctor, nurse, or other health care provider ever told you that you have any of the following health conditions?" The listed conditions included diabetes, hypertension, hyperlipidemia, asthma, depression, and anxiety disorders. Moreover, the suffering of insomnia was ascertained based on participants' responses to the ISQ. Briefly, the ISQ is a 13-item self-report instrument designed to identify insomnia according to the following three sleep-related domains: (1) the presence of a complaint of difficulty initiating or maintaining sleep, or feeling that the sleep was nonrestorative or unrefreshing; (2) the frequency of sleep-related complaints and the duration of these symptoms; and (3) the severity of daytime impairment related to the sleep complaint(s) (24). If the participant met the criteria for all three domains, they were identified as having insomnia disorder; otherwise, they were not (24).

The Berlin Questionnaire, a widely applied instrument, was used to identify subjects who were at either a high risk or a low risk for developing OSA based on three symptom categories that inquire about known risk factors for OSA (23), namely snoring behavior, sleepiness or fatigue during waking hours, and the presence of obesity (i.e., BMI $\geq$ 30 kg/m^2) or hypertension (self-reported). A "high risk for OSA" classification was assigned if the criteria for two or more categories were met, whereas a "low risk for OSA" classification was assigned if the criteria of either one or no categories was fulfilled (23).

Statistical Analysis

Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). The statistical significance level was set at $\alpha = 0.05$ for all association analyses. Descriptive analyses were conducted to calculate frequencies and proportions of categorical variables. Chi-square (χ^2) tests were used to assess whether prevalence estimates of a "high risk for OSA" differed across categories of sex, age groups, BMI, educational attainment, and monthly household income. Moreover, linear trends in the prevalence of a "high risk for OSA" classification across categories of lifestyle and behavioral factors, perceived physical health, working hours, and sleep duration were assessed using the Cochran-Armitage test for trend.

Adjusted associations were assessed by applying a modified Poisson regression with robust variance estimation using the GENMOD procedure in SAS 9.4 to estimate and infer the adjusted prevalence ratios (aPRs) and their 95% confidence intervals (CIs) (26). We evaluated the associations between being at a "high risk for OSA" (outcome variable) and cigarette smoking status, frequency of vigorous physical activity, duration of weekly television viewing, self-perceived physical health, hours of daily work, and duration of nightly sleep (exposure variables). Moreover, we evaluated the associations between being at a "high risk for OSA" (exposure variable) and health conditions (outcome variables) while statistically adjusting for the effects of demographic characteristics, as well as lifestyle and behavioral factors.

RESULTS

Description of the Study Sample

In total, 651 subjects (233 males and 418 females) were enrolled in the study, with a mean (standard deviation) age of 34.0 (9.1) years. Based on the BMI categories, 13.7% (85/620) and 8.1% (54/620) of the study participants were classified as belonging to obesity class I and obesity class II/III, respectively (**Table 1**). Moreover, most of the study participants reported having attained a university degree or higher (56.6%, 388/651; **Table 1**).

Prevalence of the "High Risk for OSA" Classification

The prevalence of a "high risk for OSA" classification, as identified by the Berlin Questionnaire, was estimated to be 20.0% (130/651; 95% CI: 16.9–23.0%) in the total study sample. The prevalence of a "high risk for OSA" classification was higher in males (24.0%) than in females (17.7%, $P = 0.053$; **Table 1**), though this difference did not gain statistical significance. Moreover, the prevalence of a "high risk for OSA" classification increased

TABLE 1 | Characteristics of study participants in the total study sample and according to the risk of obstructive sleep apnea (OSA).

Variables	Total study sample (n = 651), % (n)	High risk for OSA	
		% (n/total)	*P*-value*
Sex			
Male	35.8 (233)	24.0 (56/233)	0.053
Female	64.2 (418)	17.7 (74/418)	
Age groups (years)			
21–29	39.1 (253)	10.7 (27/253)	<0.001
30–39	37.8 (245)	17.6 (43/245)	
40–49	14.8 (96)	39.6 (38/96)	
≥50	8.3 (54)	40.7 (22/54)	
Missing, (*n*)	(3)	–	
Body mass index groups (BMI) (kg/m^2)			
Underweight/normal weight† (≤24.9)	43.7 (271)	6.6 (18/271)	<0.001
Overweight (25.0–29.9)	34.5 (214)	13.1 (28/214)	
Obesity class I (30.0–34.9)	13.7 (85)	57.7 (49/85)	
Obesity class II/III (≥35)	8.1 (50)	62.0 (31/50)	
Missing, (*n*)	(31)	–	
Educational attainment			
High school degree or less	9.2 (60)	38.3 (23/60)	<0.001
Diploma	31.2 (203)	18.7 (38/203)	
University degree or higher	59.6 (388)	17.8 (69/388)	
Monthly household income (KWD)			
<1,000	35.9 (234)	24.4 (57/234)	0.069
1,000–1,999	37.2 (242)	16.1 (39/242)	
2,000–2,999	14.5 (94)	23.4 (22/94)	
≥3,000	12.4 (81)	14.8 (12/81)	

Kg, kilograms; m^2, meter squared; KWD, Kuwaiti Dinar.

**Calculated using the chi-square test to compare proportions.*

†The underweight group (BMI < 18.5) was combined with the normal weight group (BMI between 18.5 and 24.9) because only 15 (2.4%) study participants were classified as being underweight.

with age, reaching as high as 40.7% among those aged ≥50 years ($P < 0.001$). Similarly, a "high risk for OSA" classification increased as BMI increased, with 62.0% of those classified as belonging to obesity class II/III being at "high risk for OSA" ($P < 0.001$; **Table 1**). With regard to educational attainment, the prevalence of a "high risk for OSA" classification was highest among subjects with a high school degree or less (38.3%, $P < 0.001$). However, the prevalence did not vary across income categories ($P = 0.069$; **Table 1**).

Risk Factors for a "High Risk for OSA" Classification

Table 2 shows associations between different risk factors and being considered at a "high risk for OSA." Compared with having never smoked, current smoking status was associated with a higher prevalence of being at a "high risk for OSA" (aPR = 1.58, 95% CI: 1.02–2.06). The frequency of vigorous physical activity was inversely associated with the prevalence of a "high risk for OSA" classification ($P_{trend} = 0.001$); however, after adjusting for possible confounding factors, the effect was not statistically significant (≥3 times per week vs. never/occasionally performing vigorous physical activity: aPR = 0.80, 95% CI: 0.48–1.33; **Table 2**). A longer daily duration of television viewing was associated with a higher prevalence of a "high risk for OSA" classification (≥5 h vs. <1 h per day: aPR = 1.76, 95% CI: 1.10–2.81). Moreover, lower self-perceived physical health was associated with increased prevalence of being at a "high risk for OSA" (fair/poor vs. excellent: aPR = 2.11, 95% CI: 1.15–3.87). As average daily working hours increased the prevalence of being at a "high risk for OSA" increased, with 17.5% of those who reported seven or fewer daily working hours being considered at a high risk compared to 40.0% of those who reported nine or more daily working hours ($P_{trend} < 0.001$). A longer average nightly sleep duration was associated with a reduced prevalence of a "high risk for OSA" classification (≥8 h vs. ≤6 h: aPR = 0.64, 95% CI: 0.40–0.98; **Table 2**).

Health Conditions in Relation to a "High Risk for OSA" Classification

The associations between various health conditions and being considered at a "high risk for OSA" are shown in **Table 3**. Insomnia disorder was more prevalent among subjects who were classified as being at "high risk for OSA" compared to those classified as being at "low risk for OSA" (24.6% vs. 11.7%, aPR = 2.83, 95% CI: 1.81–4.41). Moreover, a "high risk for OSA" as compared to a "low risk for OSA" was associated with a higher prevalence of diabetes (aPR = 1.94, 95% CI: 1.15–3.27), hypertension (aPR = 3.00, 95% CI: 1.75–5.16), and depression (aPR = 4.47, 95% CI: 1.80–11.08). In contrast, there was no association between the risk for OSA and hyperlipidemia, asthma, or anxiety disorders (**Table 3**).

DISCUSSION

The current study estimated the prevalence of a "high risk for OSA" classification among a working population in Kuwait for the first time, determined the associated risk factors, and identified several coexisting health conditions. This investigation showed that 20.0% of the enrolled subjects were at high risk for OSA, as measured by the Berlin Questionnaire. A high risk for OSA was more prevalent among males, older participants, obese subjects, and those with low educational attainment. Moreover, current smoking, never/occasionally being involved in vigorous physical activity, longer daily hours spent watching television, a lower level of self-perceived physical health, increased hours of daily work, and a short nightly sleep duration were associated with an increased prevalence of being classified at a high risk for OSA. Certain health conditions, including insomnia disorder, diabetes, hypertension, hyperlipidemia, and depression were more prevalent among participants classified as being at high risk for OSA compared to those at low risk for OSA.

A prior systematic review of the literature that included studies that objectively measured OSA among adults in the general population using laboratory instruments showed wide

TABLE 2 | Associations of lifestyle (behavioral) factors, perceived physical health, working hours, and sleep duration with risk of obstructive sleep apnea (OSA).

	Total Study sample, % (*n*/total)	High risk for OSA	
		% (n/total)	aPR* (95% CI)
Cigarette smoking status			
Never smoked	75.7 (493/651)	17.0 (84/493)	1.00 (Reference)
Former smoker	8.0 (52/651)	25.0 (13/52)	1.42 (0.90–2.78)
Current smoker	16.3 (106/651)	31.1 (33/106)	1.58 (1.02–2.06)†
$P^{\S}_{trend}$	–	< 0.001	–
Vigorous physical activity per week			
Never/occasionally	44.1 (287/651)	25.8 (74/287)	1.00 (Reference)
Once or twice per week	38.9 (253/651)	16.2 (41/253)	0.75 (0.55–1.03)
Three or more times per week	17.0 (111/651)	13.5 (15/111)	0.80 (0.48–1.33)
$P^{\S}_{trend}$	–	0.001	–
Daily hours of television viewing			
Less than one hour	34.6 (225/650)	14.7 (33/225)	1.00 (Reference)
More than one but less than three hours	44.2 (287/650)	21.6 (62/287)	1.19 (0.84–1.66)
More than three but less than five hours	13.2 (86/650)	22.1 (19/86)	1.46 (0.92–2.32)
Five or more hours	8.0 (52/650)	30.8 (16/52)	1.76 (1.10–2.81)‡
$P^{\S}_{trend}$	–	0.006	–
Self-perceived physical health			
Excellent	23.9 (155/648)	11.0 (17/155)	1.00 (Reference)
Very good	42.1 (273/648)	13.2 (36/273)	1.06 (0.64–1.74)
Good	28.7 (186/648)	32.3 (60/186)	1.58 (0.97–2.56)
Fair/poor	5.3 (34/648)	50.0 (17/34)	2.11 (1.15–3.87)‡
$P^{\S}_{trend}$	–	<0.001	–
Average daily hours of work			
Seven or fewer hours	73.8 (479/649)	17.5 (84/479)	1.00 (Reference)
Eight hours	20.0 (130/649)	23.1 (30/130)	0.89 (0.63–1.24)
Nine or more hours	6.2 (40/649)	40.0 (16/40)	1.49 (0.96–2.29)
$P^{\S}_{trend}$	–	<0.001	–
Average sleep duration in hours per night			
Six or fewer hours	66.8 (434/650)	24.2 (105/434)	1.00 (Reference)
Seven hours	19.1 (124/650)	9.7 (12/124)	0.44 (0.27–0.72)‡
Eight or more hours	14.1 (92/650)	14.1 (13/92)	0.64 (0.40–0.98)†
$P^{\S}_{trend}$	–	0.002	–

aPR, Adjusted prevalence ratio; CI, Confidence interval.
**Adjusted for sex, age, body mass index, educational attainment, monthly household income, and all variables shown in the table. †P < 0.05. ‡P < 0.01. §Calculated using the Cochran-Armitage test for a trend in proportions.*

TABLE 3 | Associations of obstructive sleep apnea (OSA) risk with comorbid health conditions.

Health condition	Risk for OSA		aPR* (95% CI)	*P*-value
	Low risk, % (*n*/total)	High risk, % (*n*/total)		
Insomnia	11.7 (61/521)	24.6 (32/130)	2.83 (1.81–4.41)	< 0.001
Diabetes	6.4 (33/520)	16.2 (22/130)	1.94 (1.15–3.27)	0.012
Hypertension	5.8 (30/520)	33.9 (44/130)	3.00 (1.75–5.16)	< 0.001
Hyperlipidemia	15.0 (78/520)	26.9 (35/130)	1.12 (0.76–1.67)	0.564
Asthma	12.7 (66/520)	13.9 (18/130)	1.49 (0.78–2.89)	0.229
Depression	4.0 (21/521)	7.7 (10/130)	4.47 (1.80–11.08)	0.001
Anxiety disorders	8.5 (44/520)	13.1 (17/130)	1.41 (0.70–2.83)	0.331

aPR, Adjusted prevalence ratio; CI, Confidence interval.
**Adjusted for sex, age, body mass index, educational attainment, monthly household income, cigarette smoking status, vigorous physical activity status, daily hours of television viewing, self-perceived physical health, average daily hours of work, and average nightly sleep duration in hours.*

variations in the prevalence of OSA, with estimates of mild OSA (AHI ≥ 5 to <15) ranging from 9 to 38%, and estimates of moderate-to-severe OSA (AHI ≥15) varying from 6 to 17% (9). Another systematic review focusing on studies published among Asian adults reported that OSA prevalence ranged from 3.7 to 97.3% (27). At the regional level, a study based on a large sample of Saudi school employees estimated the prevalence of OSA to be 8.8% (12.8% in men and 5.1% in women) based on polysomnography assessments (28). Such a wide variability in the reported prevalence of OSA can be partially explained by the method of ascertainment (objective [laboratory-based] vs. subjective [questionnaire-based]) and the study population's risk for OSA (i.e., pretest probability of OSA). In the current study, 20.0% of the participants were identified as being at high risk for OSA according to the Berlin Questionnaire criteria. This estimate is within the mild OSA prevalence range (9% to 38%) reported by Senaratna et al. (9). Moreover, our estimate is consistent with previously reported OSA prevalence estimates in general adult populations from studies that used the Berlin Questionnaire to ascertain OSA risk status. For example, the results of the National Sleep Foundation *Sleep in America 2005* poll showed that 26% of the study participants met the Berlin Questionnaire criteria for a high risk for OSA (29). Moreover, a nationwide survey conducted among the Korean adult population reported that 15.8% of the participants were classified as being at high risk for OSA based on the same Berlin Questionnaire definition (30). In a primary health care setting, a study conducted in the United Arab Emirates estimated the prevalence of a high risk for OSA to be 20.9% using the Berlin Questionnaire criteria (31). Nevertheless, comparing OSA prevalence estimates between populations should be interpreted with caution, as characteristics of study subjects and ascertainment methods could contribute to the observed inter-population heterogeneity.

In this report, a higher prevalence of a high risk for OSA was observed among male (sex-based difference did not gain statistical significance), older aged, and obese participants, which is in agreement with the existing literature (4–6, 32). Moreover, current smoking status compared to never having smoked was associated with an increased prevalence of being classified at a high risk for OSA among our study participants. This observation has been reported previously and is hypothesized to be explained by the potential health-related changes caused by smoking, including increases in sleep instability and airway inflammation (6, 15, 33). With regard to protective factors, we observed a lower prevalence of being classified at a high risk for OSA among participants who reported regular

engagement in vigorous physical activity compared to those who were never/occasionally involved in such activities. This observation further highlights the positive effects of physical activity on general health and OSA risk. An analysis based on the Ontario Health Study reported that increased levels of vigorous-intensity activity and walking were associated with reduced OSA risk (34), which further corroborates our observation. In contrast, an increased number of daily hours spent watching television was associated with a higher prevalence of a "high risk for OSA" in the current report, even after adjusting for potential confounding factors, including obesity status. Increased television viewing is probably a surrogate marker of a sedentary lifestyle and unhealthy dietary intake (35, 36). Interestingly, we observed a positive association between the average number of daily hours spent working and a high risk for OSA, where those reporting at least nine daily hours of work had the highest prevalence of OSA risk. Such an observation could be explained by the potentially fewer hours spent sleeping among those performing longer work hours; however, the observed association was independent of the average number of nightly sleep hours reported by the participants. Hence, the factors underlying this observation warrant further investigation. Moreover, we reported that the prevalence of being at a high risk for OSA decreased as the average nightly sleep duration increased. In line with our observation, a prior study showed that the average sleep duration of the group at high risk for OSA (7.0 ± 1.4 h) was shorter than that of subjects in the group at low risk for OSA (7.4 ± 1.2 h, $P < 0.001$) (30). These observations further highlight the fact that reduced sleep duration is a characteristic of OSA that can lead to adverse health outcomes. A study from Muscat, Oman reported a high prevalence of relatively short night sleep duration (<7 h), which authors have indicated that such a nocturnal sleep duration is culturally influenced and is related to sleep patterns and behaviors that have been adapted recently by people in the region (37).

The current analysis also showed that being classified at a high risk for OSA was associated with several comorbid conditions. For instance, insomnia disorder was 2.83-times more prevalent among subjects at high risk for OSA compared to those at low risk for OSA. This observation is in agreement with prior investigations that indicated that the co-occurrence of insomnia disorder and OSA is common based on a large global meta-analysis (38). Also, we observed that subjects who were at high risk for OSA, compared to those at low risk for OSA, had a higher prevalence of diabetes (16.2 vs. 6.4%). This finding is also consistent with results of a meta-analysis of cohort studies that estimated the pooled relative risk for the association between OSA risk and diabetes development to be 1.40 (95% CI: 1.32–1.48) (39). The same meta-analysis reported a dose-effect relationship between the AHI value and diabetes risk (39). We also observed an association between OSA risk and hypertension, which is in agreement with prior investigations that have shown an increased risk of hypertension and cardiovascular disease among subjects with OSA (40, 41). In regard to psychological disorders, a higher prevalence of depression was reported by subjects classified as being at high risk for OSA compared to those at low risk for OSA. Although this observation has been reported previously, the directionality of this association remains unclear (20, 42). In general, the co-occurrence of health conditions with OSA can be partially explained by certain shared risk factors and pathophysiology; nevertheless, more investigations are needed to better understand the underlying mechanisms.

The strength of the current study was the enrollment of working subjects, which could more closely reflect the OSA burden in the general population than a clinical-based study sample. Moreover, recruiting participants from different places of work increased the representativeness of our sample. Nevertheless, non-probability-based sampling (i.e., convenience sampling) may limit the generalizability of our results. For instance, the proportion of female participants was higher than the proportion of male participants in our study sample (64.2 vs. 35.8%). Such a sex-related self-selection bias may reduce the external validity of our findings, but not the internal validity of the study. A further limitation was the questionnaire-based ascertainment of the participants' OSA risk status. We did, however, use the Berlin Questionnaire to do so, which a meta-analysis has shown to be an acceptable instrument for OSA ascertainment, with a pooled sensitivity of 0.76 (95% CI: 0.71–0.81) and pooled specificity of 0.59 (0.48–0.66) as compared to a laboratory-based assessment of OSA (13). Such results demonstrate an acceptable accuracy; however, misclassification of OSA risk in large epidemiologic studies using questionnaire-based assessments is inevitable; however, our estimated prevalence of being at a high risk for OSA is close to reported estimates from other countries, as were the associations we reported. This is an indication that the misclassification of OSA risk status, if any, was not substantial and did not influence the study's results. Moreover, selection bias cannot be excluded in cross-sectional studies; more specifically, self-selection bias, which can occur when more susceptible individuals participate in a study. It is also essential to note that our analysis aimed to assess concurrent associations between OSA risk status and different risk factors and health conditions, not to infer causal or temporal relationships.

In conclusion, this study is the first to estimate the prevalence of OSA risk among a working population in Kuwait and to assess its risk factors and comorbid conditions among this population. The findings of our study indicated that 1/5 of working adults are at high risk for OSA, which depends on an individual's personal characteristics and lifestyle factors. For instance, modifiable risk factors associated with elevated OSA prevalence included smoking, sedentary lifestyle (no physical activity and increased television viewing), increased working hours, and short nightly sleep duration. In addition, we demonstrated that being at high risk for OSA was associated with multiple coexisting health conditions, such as insomnia disorder, diabetes, hypertension, and depression. Overall, the results of this study demonstrated that OSA is common among a sample of working adults in Kuwait and is associated with elevated morbidity. To guide public health prevention efforts, future studies are needed to corroborate our findings and to assess the burden of OSA in different settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Health Sciences Center Ethics Committee for Student Research at Kuwait University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HA-Q and HA-O conceptualized and designed the study, designed the data collection instrument, collected data, analyzed and interpreted the data, and drafted the manuscript. KA-H, FA-M, MA-M, and MA-A conceptualized and designed the study, designed the data collection instrument, collected data, contributed to data analysis and interpretation, and critically reviewed and revised the manuscript for important intellectual content. AM and AA contributed to conceptualization and design of the study, contributed to data analysis and interpretation, and critically reviewed and revised the manuscript for important intellectual content. AZ contributed to conceptualization and design of the study, contributed to designing the data collection instrument, supervised data collection, contributed to data analysis and interpretation, and critically reviewed and revised the manuscript for important intellectual content. All authors have reviewed, revised, and approved the final manuscript.

ACKNOWLEDGMENTS

We are sincerely grateful to the participants and the staff at the recruitment sites for helping with study logistics.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.620799/full#supplementary-material

REFERENCES

1. Ramar K, Olson EJ. Management of common sleep disorders. *Am Fam Physician.* (2013) 88:231–8.
2. Szentkiralyi A, Madarasz CZ, Novak M. Sleep disorders: impact on daytime functioning and quality of life. *Expert Rev Pharmacoecon Outcomes Res.* (2009) 9:49–64. doi: 10.1586/14737167.9.1.49
3. Colten HR, Altevogt BM. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington, DC: National Academies Press (2006).
4. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Prog Cardiovasc Dis.* (2009) 51:285–93. doi: 10.1016/j.pcad.2008.08.001
5. Rundo JV. Obstructive sleep apnea basics. *Cleve Clin J Med.* (2019) 86:2–9. doi: 10.3949/ccjm.86.s1.02
6. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med.* (2002) 165:1217–39. doi: 10.1164/rccm.2109080
7. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. *JAMA.* (2020) 323:1389–400. doi: 10.1001/jama.2020.3514
8. Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. *Nat Sci Sleep.* (2018) 10:21–34. doi: 10.2147/NSS.S124657
9. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev.* (2017) 34:70–81. doi: 10.1016/j.smrv.2016.07.002
10. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med.* (2015) 3:310–8. doi: 10.1016/S2213-2600(15)00043-0
11. Coughlin K, Davies GM, Gillespie MB. Phenotypes of obstructive sleep apnea. *Otolaryngol Clin North Am.* (2020) 53:329–38. doi: 10.1016/j.otc.2020.02.010
12. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. *Can J Anaesth.* (2010) 57:423–38. doi: 10.1007/s12630-010-9280-x
13. Chiu HY, Chen PY, Chuang LP, Chen NH, Tu YK, Hsieh YJ, et al. Diagnostic accuracy of the Berlin questionnaire, STOP-BANG, STOP, and Epworth sleepiness scale in detecting obstructive sleep apnea: a bivariate meta-analysis. *Sleep Med Rev.* (2017) 36:57–70. doi: 10.1016/j.smrv.2016.10.004
14. Amra B, Rahmati B, Soltaninejad F, Feizi A. Screening questionnaires for obstructive sleep apnea: an updated systematic review. *Oman Med J.* (2018) 33:184–92. doi: 10.5001/omj.2018.36
15. Gharibeh T, Mehra R. Obstructive sleep apnea syndrome: natural history, diagnosis, and emerging treatment options. *Nat Sci Sleep.* (2010) 2:233–55. doi: 10.2147/NSS.S6844
16. Jehan S, Masters-Isarilov A, Salifu I, Zizi F, Jean-Louis G, Pandi-Perumal SR, et al. Sleep Disorders in Postmenopausal Women. *J Sleep Disord Ther.* (2015) 4:1–8. doi: 10.4172/2167-0277.1000212
17. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA.* (2004) 291:2013–6. doi: 10.1001/jama.291.16.2013
18. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc.* (2008) 5:136–43. doi: 10.1513/pats.200709-155MG
19. Andre S, Andreozzi F, Van Overstraeten C, Ben Youssef S, Bold I, Carlier S, et al. Cardiometabolic comorbidities in obstructive sleep apnea patients are related to disease severity, nocturnal hypoxemia, and decreased sleep quality. *Respir Res.* (2020) 21:35. doi: 10.1186/s12931-020-1284-7
20. Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, et al. Obstructive sleep apnea, depression and cognitive impairment. *Sleep Med.* (2020) 72:50–8. doi: 10.1016/j.sleep.2020.03.017
21. Rajan P, Greenberg H. Obstructive sleep apnea as a risk factor for type 2 diabetes mellitus. *Nat Sci Sleep.* (2015) 7:113–25. doi: 10.2147/NSS.S90835
22. Weiderpass E, Botteri E, Longenecker JC, Alkandari A, Al-Wotayan R, Al Duwairi Q, et al. The prevalence of overweight and obesity in an adult kuwaiti population in 2014. *Front Endocrinol (Lausanne).* (2019) 10:449. doi: 10.3389/fendo.2019.00449
23. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* (1999) 131:485–91. doi: 10.7326/0003-4819-131-7-199910050-00002
24. Okun ML, Kravitz HM, Sowers MF, Moul DE, Buysse DJ, Hall M. Psychometric evaluation of the Insomnia Symptom Questionnaire: a self-report measure to identify chronic insomnia. *J Clin Sleep Med.* (2009) 5:41–51. doi: 10.5664/jcsm.27391
25. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation (WHO Technical Report Series 894), Report No.: 894.* (2000). p. 253.

26. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* (2004) 159:702–6. doi: 10.1093/aje/kwh090
27. Mirrakhimov AE, Sooronbaev T, Mirrakhimov EM. Prevalence of obstructive sleep apnea in Asian adults: a systematic review of the literature. *BMC Pulm Med.* (2013) 13:10. doi: 10.1186/1471-2466-13-10
28. Wali SO, Abalkhail B, Krayem A. Prevalence and risk factors of obstructive sleep apnea syndrome in a Saudi Arabian population. *Ann Thorac Med.* (2017) 12:88–94. doi: 10.4103/1817-1737.203746
29. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population: results from the national sleep foundation sleep in America 2005 poll. *Chest.* (2006) 130:780–6. doi: 10.1378/chest.130.3.780
30. Sunwoo JS, Hwangbo Y, Kim WJ, Chu MK, Yun CH, Yang KI. Prevalence, sleep characteristics, and comorbidities in a population at high risk for obstructive sleep apnea: a nationwide questionnaire study in South Korea. *PLoS ONE.* (2018) 13:e0193549. doi: 10.1371/journal.pone.0193549
31. Mahboub B, Afzal S, Alhariri H, Alzaabi A, Vats M, Soans A. Prevalence of symptoms and risk of sleep apnea in Dubai, UAE. *Int J Gen Med.* (2013) 6:109–14. doi: 10.2147/IJGM.S40001
32. Al-Abri M, Al-Hashmi K, Jaju D, Al-Rawas O, Al-Riyami B, Hassan M. Gender difference in relationship of apnoea/hypopnoea index with body mass index and age in the omani population. *Sultan Qaboos Univ Med J.* (2011) 11:363—8.
33. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. *Arch Intern Med.* (1994) 154:2219–24. doi: 10.1001/archinte.154.19.2219
34. Hall KA, Singh M, Mukherjee S, Palmer LJ. Physical activity is associated with reduced prevalence of self-reported obstructive sleep apnea in a large, general population cohort study. *J Clin Sleep Med.* (2020) 16:1179–87. doi: 10.5664/jcsm.8456
35. Blass EM, Anderson DR, Kirkorian HL, Pempek TA, Price I, Koleini MF. On the road to obesity: television viewing increases intake of high-density foods. *Physiol Behav.* (2006) 88:597–604. doi: 10.1016/j.physbeh.2006.05.035
36. Swinburn B, Shelly A. Effects of TV time and other sedentary pursuits. *Int J Obes (Lond).* (2008) 32 Suppl 7:S132–6. doi: 10.1038/ijo.2008.249
37. Al-Abri MA, Al Lawati I, Zadjali F, Ganguly S. Sleep patterns and quality in omani adults. *Nat Sci Sleep.* (2020) 12:231–7. doi: 10.2147/NSS.S233912
38. Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing YK, et al. Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev.* (2019) 45:1–17. doi: 10.1016/j.smrv.2019.01.004
39. Qie R, Zhang D, Liu L, Ren Y, Zhao Y, Liu D, et al. Obstructive sleep apnea and risk of type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of cohort studies. *J Diabetes.* (2020) 12:455–64. doi: 10.1111/1753-0407.13017
40. Salman LA, Shulman R, Cohen JB. Obstructive sleep apnea, hypertension, and cardiovascular risk: epidemiology, pathophysiology, and management. *Curr Cardiol Rep.* (2020) 22:6. doi: 10.1007/s11886-020-1257-y
41. Bangash A, Wajid F, Poolacherla R, Mim FK, Rutkofsky IH. Obstructive sleep apnea and hypertension: a review of the relationship and pathogenic association. *Cureus.* (2020) 12:e8241. doi: 10.7759/cureus.8241
42. Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. *Sleep Med Rev.* (2009) 13:437–44. doi: 10.1016/j.smrv.2009.04.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 22 July 2021
doi: 10.3389/fpsyt.2021.642333

The Different Facets of Heart Rate Variability in Obstructive Sleep Apnea

Hua Qin[1], Nicolas Steenbergen[2], Martin Glos[1], Niels Wessel[3], Jan F. Kraemer[3], Fernando Vaquerizo-Villar[4,5] and Thomas Penzel[1,6]**

[1] Interdisciplinary Center of Sleep Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany, [2] Imperial College London School of Medicine, London, United Kingdom, [3] Department of Physics, Humboldt Universität zu Berlin, Berlin, Germany, [4] Biomedical Engineering Group, Universidad de Valladolid, Valladolid, Spain, [5] Centro de Investigación Biomédica en Red-Bioingeniería, Biomateriales y Nanomedicina, Valladolid, Spain, [6] Saratov State University, Russian Federation, Saratov, Russia

Obstructive sleep apnea (OSA), a heterogeneous and multifactorial sleep related breathing disorder with high prevalence, is a recognized risk factor for cardiovascular morbidity and mortality. Autonomic dysfunction leads to adverse cardiovascular outcomes in diverse pathways. Heart rate is a complex physiological process involving neurovisceral networks and relative regulatory mechanisms such as thermoregulation, renin-angiotensin-aldosterone mechanisms, and metabolic mechanisms. Heart rate variability (HRV) is considered as a reliable and non-invasive measure of autonomic modulation response and adaptation to endogenous and exogenous stimuli. HRV measures may add a new dimension to help understand the interplay between cardiac and nervous system involvement in OSA. The aim of this review is to introduce the various applications of HRV in different aspects of OSA to examine the impaired neuro-cardiac modulation. More specifically, the topics covered include: HRV time windows, sleep staging, arousal, sleepiness, hypoxia, mental illness, and mortality and morbidity. All of these aspects show pathways in the clinical implementation of HRV to screen, diagnose, classify, and predict patients as a reasonable and more convenient alternative to current measures.

Keywords: obstructive sleep apnea, heart rate variability, autonomic dysfunction, central autonomic networks, time-window analysis, time-domain analysis, frequency-domain analysis, non-linear analysis

OPEN ACCESS

Edited by:
Carolina Lombardi, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Frederic Roche, Université Jean Monnet, France
Vitor Engracia Valenti, São Paulo State University, Brazil

****Correspondence:***
Hua Qin
hua.qin@charite.de
Thomas Penzel
thomas.penzel@charite.de

Specialty section:
This article was submitted to Sleep Disorders, a section of the journal Frontiers in Psychiatry

Received: *15 December 2020*
Accepted: *14 June 2021*
Published: *22 July 2021*

Citation:
Qin H, Steenbergen N, Glos M, Wessel N, Kraemer JF, Vaquerizo-Villar F and Penzel T (2021) The Different Facets of Heart Rate Variability in Obstructive Sleep Apnea. Front. Psychiatry 12:642333. doi: 10.3389/fpsyt.2021.642333

INTRODUCTION

Obstructive sleep apnea (OSA) is closely associated with neurocognitive, behavioral, psychophysiological states, and cardiovascular outcomes (1–3). It is estimated that globally ∼1 billion adults have mild to severe sleep apnea. Some countries have a prevalence over 50% and it still is increasing. The consequent health and financial burden can be minimized by effective diagnosis and treatment (4). To that effect, recently, the role of cardiovascular autonomic dysfunction has received increasing attention as an independent risk factor for clinical complications in OSA (5). Heart rate variability (HRV) has been generally accepted as a non-invasive tool to quantify cardiovascular autonomic modulation under varying healthy and pathogenic conditions (6, 7). HRV measures the variation between beat-to-beat intervals over a time series (6). It is an integrated reflection of central-peripheral neural feedback mechanisms to the heart *via* mediating sympathovagal inflow and outflow (8). Previous studies suggested that in conjunction with brain imaging, HRV analysis has been used to investigate the connection between autonomic cardiac modulation and sleeping brain activity (9).

Currently, HRV analysis, including time-domain, frequency-domain, and non-linear analysis, is used to explore the activities of sympathetic and parasympathetic nervous systems (6, 10). Time-domain analysis quantifies the magnitudes of variation. The most relevant time-domain parameters are described in **Table 1**. For example, the standard deviation of normal-to-normal intervals (SDNN), a global HRV metric, is frequently used as a prognostic indicator of cardiovascular risk in different populations (11). Frequency-domain analysis is used for partitioning the rhythms of electrocardiography (ECG) signals into different frequencies (12, 13). This analysis helps gain a better understanding of cardiac control as ECG frequencies could be related to intrinsic elements modulated by the cardiac autonomic system alone. Power spectral density (PSD) is the standard method employed to estimate the distribution of the HRV signal power over frequency. **Table 2** shows the main frequency-domain parameters typically computed from the PSD of HRV (14). High frequency (HF) components mainly present parasympathetic activity. However, there is a disagreement with regards to the low frequency (LF) components. Some studies suggested that LF, when expressed in normalized units, is a quantitative marker of sympathetic modulation, but other studies view LF as a reflection of both sympathetic and vagal activity mainly mediated by the baroreflex. Thus, the LF/HF ratio is considered a detection index for either sympathovagal balance or sympathetic modulations (15). Apart from the conventional PSD, other frequency-domain methods are also used to analyze the frequency content of the HRV, such as high order spectral analysis and wavelet analysis. Non-linear HRV captures dynamic sequences of the heartbeat time series related to randomness and self-similarity (10, 16). It is suggested that non-linear fluctuations result from interactions of electrophysiological, hemodynamic, and humoral variables, as well as by autonomic and central nervous regulation (17). Pathologically monotonous and erratic HRV patterns are associated with negative outcomes in cardiac patients (18). OSA patients show a reduced dynamic complexity (19, 20). The clinical relevance of non-linear HRV in OSA still needs to be the established. **Table 3** summarizes the reported non-linear parameters and methods in current studies on HRV (6, 14, 21). However, this not by any means an exhaustive list.

Heart rate and blood pressure oscillations are characterized by parasympathetic predominance and sympathetic inhibition in normal subjects during non-rapid eye movement (NREM) sleep (22). In contrast, sympathetic predominance and parasympathetic withdrawals are found during similar rapid eye movement (REM) sleep and wakefulness. As a result, there is a reduction of heart rate and blood pressure during NREM sleep and an increase during REM sleep. However, patients with OSA manifest a heterogeneous pathophysiology (e.g., upper airway anatomical collapsibility, loop gain, arousal threshold, and upper airway gain) and characteristics (e.g., recurrent apnea and hypopnea, nocturnal hypoxemia, frequent awakenings, and daytime sleepiness) (23). Consequently, hypoxia and arousal in OSA are thought to potentially be the main factors leading to certain hemodynamic instability, causing fluctuations in heart rate that contribute to the changes in HRV. Previous studies have shown the detrimental effect of OSA on HRV either during wakefulness or sleep (24–26), suggesting a relationship between OSA severity and cardiovascular autonomic modulations using conventional HRV analysis. Additionally, (27). suggested that prolonged alterations in autonomic function existed even in snoring subjects. Those findings highlighted the potential cumulative impacts of OSA on HRV. On the other hand, Idiaquez et al. (28) found independent pathophysiological mechanisms may underlie the modulation of neurobehavioral changes and HRV in OSA despite sharing common cerebral control regions and mediated pathways. Although the HRV time window is more related to mathematics, physics and statistics, its determination in OSA-related events (e.g., sleep apnea, arousal, and periodic limb movement) is crucial in reflecting the relationship between autonomic changes and OSA-related physiological changes. Furthermore, it allows for the discovery of how the cardiovascular, respiratory, autonomic, and central nervous systems interact with each other in OSA. The HRV time window is also particularly important in coupling analysis such as synchronization and ensemble symbolic coupling, potentially

TABLE 1 | Selected time-domain HRV measures.

Variable	Units	Definition
Time-domain analysis		
SDNN	ms	Standard deviation of normal to normal (NN) interval time series
SDANN*X (X = 1, 5)*	ms	Standard deviation of BBI averages in successive X-minute intervals
RMSSD	ms	Square root of the mean squared differences of successive NN intervals
pNN*X (X = 50, 100, 200)*	%	NN>Xms counts divided by the total number of all NN intervals.
pNNI*X (X = 10, 20, 30)*	%	NN<Xms counts divided by the total number of all NN intervals.
Time-domain geometric measures		
HRVi	–	HRV triangular index
TINN	ms	Baseline width of the minimum square difference triangular interpolation of the NN interval histogram

TABLE 2 | Selected frequency-domain HRV parameters.

Variable	Units	Definition
Frequency-domain analysis		
TP	ms^2	Total power (0–0.4 Hz)
ULF	ms^2	Ultra-low frequency (0–0.01 Hz)
VLF	ms^2	Very low frequency (0.01–0.04 Hz)
LF	ms^2	Low frequency (0.04–0.15 Hz)
HF	ms^2	High frequency (0.15–0.4 Hz)
LF/HF	–	Ratio of LF to HF
HF nu	–	Normalized high frequency power HF/(LF+HF)×100
LF nu	–	Normalized low frequency power LF/(LF+HF)×100

TABLE 3 | Selected non-linear HRV parameters and methods.

Variable	Units	Definition
Chaotic invariant analysis		
D_2	–	Correlation dimension
LLE	–	Largest Lyapunov exponent
FD	–	Fractal dimension
H	–	Hurst exponent
Poincare plots		
SD1	ms	Standard deviation around the Y-axis of the Poincaré plot
SD2	ms	Standard deviation around the X-axis of the Poincaré plot
Detrended fluctuation analysis (DFA)		
α_1	–	Slope of the short-time scales of the DFA profile
α_2	–	Slope of the long-time scales of the DFA profile
Entropy analysis		
ApEn	–	Approximate entropy
SampEn	–	Sample entropy
RenyiEn	–	Renyi entropy
ShanEn		Shannon entropy
REEn	–	Renormalized entropy
Recurrence plots (RP)		
MDL	–	Average length of diagonal lines in RP
TT	–	Average length of vertical lines in RP
DET	–	Rercentage of recurrent points forming diagonal lines in a RP
LAM	–	Rercentage of recurrent points forming vertical lines in a RP
ENTR	–	Shannon entropy of the distribution of diagonal lines in a RP
Symbolic dynamics		
Fwshannon	–	Shannon entropy of the probabilities of occurrence of the words of the symbol sequence
Forbword	–	Number of words of length 3 that never or only seldom occur
Wsdavar	–	Standard deviation of the word sequence
Phvar5	–	Portion of high-variability patterns in the NN interval time series (>5ms)
Plvar20	–	Portion of low-variability patterns in the NN interval time series (<20ms)
WpsumXY (XY = 02, 13)	–	Percentage of words which contain the symbols "X" and "Y"

revealing direction and strength of dynamic cardiovascular transition (29, 30).

Taken together, HRV could provide a static and a dynamic perspective to observe the changes in connectivity between central and cardiac autonomic modulation during sleep and its persistent influence during daytime. This review focuses on neuro-cardiac autonomic regulatory mechanisms and the multifaceted applications of HRV in OSA as a potential additional clinical diagnostic tool.

TIME-WINDOW ANALYSIS TECHNOLOGY OF HRV

HRV is usually measured over a short-term (5–15 min) or long-term period (1–24 h). Long-term measurements are generally used to assess mortality and adverse prognosis of patients, but short-term measurements have been shown to be sufficiently stable and applicable for screening. However, 5-min recordings only had strong correlation with HF (31). Li et al. (32) assessed short-term analysis to be suitable for estimation of autonomic status and tracking dynamic changes but long-term changes to be better as an autonomic function assessor and prognostic indicator. The issue is that the cardiovascular system is in constant flux and thus HRV parameters constantly fluctuate at rest or during various conditions (33–35). The selection of the time window is thus a crucial aspect in HRV analysis (36, 37).

Most studies use short-term time windows with their analytic techniques; 2–5 min with Fast Fourier Transform (FFT) or autoregression, or 1–2 min with multiple trigonometric regressive spectral (MTRS) analysis (6, 38, 39). New techniques such as short time Fourier transform or Wigner-Ville transforms (WVT) are able to return instant power spectral profiles (40, 41). Short-term windows have the advantages of being easy to perform, easy to control for confounding factors, require the least data processing and describe dynamic HRV changes in short time periods (32). However, the constant flux of HRV values means that it may not be stable and that it cannot measure long RRI fluctuations, especially the ultra-LF (6, 37). Ultra-short term HRV has shown potential for diagnostic capability within a short timespan immediately after an apneic event (e.g., arousals). However, it is only able to measure time-domain parameters and no frequency-domain parameters, severely limiting its informational output and, like short-term HRV, the constant flux may mean it is unstable (42).

Longer time windows are commonly analyzed with FFT or autoregression, as they are commonly divided into 1–5-min periods and averaged to provide a mean for the total time segment (6, 36, 37). Alternatively, the entire time window is used as a single data segment, which yields similar results for LF and HF over 24 h (43). Its primary advantage is in collecting stable and reflective ECG data over an extended period of time. Any singular 5-min window can vary wildly from another, and thus measuring HRV over a whole day allows for better estimations of fluctuations (32). However, long-term HRV analysis is financially expensive and labor intensive, on top of requiring more considerations about filtering and analysis (6, 37).

Li et al. (32) suggest three main uses of HRV analysis: evaluating autonomic function in specific populations, describing changes in autonomic function, and prognosis. To evaluate autonomic function in specific conditions such as myocardial infarction (MI), hypertension and Parkinson's, short-term analysis may be used (44–47). Long-term analysis can be used for daytime or sleep analysis, or a full 24-h analysis and is thus more suitable for assessing OSA autonomic status, in line with what most studies use. Although HRV analyses of different window lengths are closely correlated, they do not always align

(48–50). Studies in this particular area are particularly lacking and require further investigation. In describing change in autonomic function, both short-term and long-term analysis can be used over a period of hours or months, whereas short-term can measure changes in minutes. In this regard, measuring changes due to apneic episodes is a useful application of short-term analysis. However, this type of short-term analysis likely already falls under an overnight long-term analysis (32). Many OSA studies use overnight HRV with 5-min time windows. Still, more studies are needed directly comparing the two with respect to OSA. Using HRV as a prognostic indicator is usually done *via* long-term analysis. Many studies assessing mortality have used overnight or 24-h HRV analyses to obtain a reliable prognosis and use 5-min windows within these time periods to compare HRV (49–55).

It is clear that the majority studies use long-term HRV analysis for the assessment of OSA, mostly with time-frequency domains. However, whether this is the best use of HRV is not clear as there is a lack of studies reporting on this particular aspect. To further this point, there is no agreement on a single method with which to analyze HRV in sleep apnea as a wide variety of time windows within an overnight sleep study are analyzed in the literature. Studies aimed at short-term changes potentially analyze 2-min epochs around apneas and hypopneas or arousal-free windows or look at the first and last 10-min segments during SDB and stable breathing during NREM, for example (56–58). Long-term analysis aimed studies sometimes look at averaged consecutive 5-min windows in different sleep stages (stage 2 is commonly used as a reflection of NREM sleep) or stable 5-min intervals from each sleep stage or the first 5-min segment of each sleep stage, to name a few (59). The standardization of time window approach to provide a regulated and agreed upon methodology of time window analysis that presents comparable and valuable ECG changes in OSA during an overnight sleep study is an area in pressing need of further study. Although time window analysis is a potent area of research to solidify first, the current use of HRV has shown promise and accuracy in many areas, from prognosis to sleep stage detection.

TECHNICAL FEATURES OF HRV MEASUREMENTS

There are some important technical features that affect HRV analysis. In this respect, ECG sampling rate could be critical to the accuracy and reliability of the HRV time series. Two hundred and fifty hertz or higher are recommended, however, given the minor relative errors among various ECG sampling rates, over 100 Hz are acceptable in time-domain, frequency-domain, and non-linear HRV analysis (60–62). Concerning the extraction of RR intervals, there is a big variety of algorithms aimed at detecting the R peaks (63), being the Pan and Tompkins the most well-known one (64). However, artifacts and ectopic beats are usually present in ECG recordings, which can result in non-normal RR intervals, thus affecting HRV analysis. This issue is addressed by detecting and correcting non-normal beats. The detection of non-normal beats can be performed using different automatic methods: time and morphological approaches, methods based on the morphological transformation, wavelet-based approaches, empirical mode decomposition methods, and neural network approaches (65). Conversely, deletion, interpolation (zero-degree, linear interpolation, and cubic spline methods), and adaptive approaches are used to correct non-normal beats (65). However, these methods can also cause measurement errors in the HRV signal, which demands more research efforts on the development of correction methods.

INFLUENCE OF SLEEP STRUCTURE ON HRV

According to the American Academy of Sleep Medicine (AASM), sleep is categorized into non-rapid eye movement (NREM) stages N1, N2, N3, into stage rapid eye movement sleep (REM), and into stage Wake by visual electroencephalogram (EEG), electrooculogram (EOG), and chin electromyogram (EMG) scoring (66). Collectively, studies have reported a general trend in HRV during healthy sleep; LF and the LF/HF ratio are high in Wake and decrease in NREM sleep, peaking once more during REM sleep, while HF follows the opposite trend (67–71). This corresponds to muscle sympathetic and parasympathetic activity observed in sleep (72, 73). Opposingly, Ako et al. (74) reported decreasing LF and LF/HF ratio during NREM and an increase during REM but no differentiation of HF during the NREM and REM stages in healthy sleep. However, Abdullah et al. (75) reported a strong correlation between EEG delta, sigma, and beta bands with HRV parameters (LF, HF, LF/HF ratio). Jurysta et al. (76) and Köhler and Schönhofer (77) reported negative correlations between cardiac vagal predominance and delta sleep EEG and abnormalities in the respective power bands. In contrast, Yang et al. (71) reported a negative relation between cardiac sympathetic regulation and depth of sleep, but not vagal regulation. The repeatability of the measurements in HRV parameter patterns in relation to the sleep stages, however, certifies the suggested physiological activity seen during sleep.

INFLUENCE OF SLEEP APNEA ON HRV DURING DAYTIME

OSA seems to have long-term effect on HRV even during wakefulness with the absence of sleep apnea. Limited data regarding its underlying mechanisms during daytime or ambulatory wake state is reported. It is assumed that autonomic dysfunction plays a key role in persistent OSA related outcomes, leading to a blunted diurnal HRV pattern. Using 10-min ECG segments and muscle sympathetic nerve activity (MSNA) recordings during daytime, Narkiewicz et al. found that the magnitude of cardiovascular variability is associated with the severity of OSA. There was reduced RR variance, increased sympathetic tone and decreased parasympathetic tone in moderate-to-severe OSA populations compared to matched controls (25). Balachandran et al. (78) found significantly different LF, HF, and LF/HF between mild OSA without any symptoms and healthy controls in waking condition. Similarly,

Hilton et al. (79) found that at daytime amount of HF power as marker of vagal activity is negatively correlated with the apnea-hypopnea index (AHI) and %HF and LF/HF were shown to be different in OSA patients compared to controls. Respiratory sinus arrhythmia (RSA) is a natural physiological phenomenon reflecting cardiopulmonary coupling characterized by periodic increases and decreases with heartbeat synchronized with respiration, whereby heartbeat increases during inspiration and decreases during expiration. Consequently, normal respiration HRV is different than deep respiration HRV and apneic respiration HRV due to the inspiration-expiration pattern (80). Given the altering effect of respiration on HRV, Khoo et al. (81) developed two modified spectral HRV measures (the modified LF/HF and the average gain relating respiration to RR changes) to show cardiac autonomic alternations in OSA and non-OSA during in relaxed wakefulness and stage 2 sleep compared to standard spectral metrics. They found that the modified spectral HRV measures are more sensitive than the traditional measures, suggesting a respiration–correlated component should be considered in HRV analysis. In addition, Wang et al. (24) suggested that autonomic dysfunction was related to OSA severity. However, they mainly evaluated gender differences in frequency-domain HRV measures, rather than with different levels of severity of OSA, showing significantly higher LF in male patients from wakefulness to sleep state. Park et al. (82) examined the correlation between severity of OSA and overnight HRV during wakefulness in moderate/severe OSA. They found increased total power (TP), LF, LF/HF, and HRV triangular index in the severe group compared to the moderate one. Comparably, Qin et al. (83) found a significant relationship between 5-min HRV measures during wakefulness prior to sleep onset and OSA severity in a large international clinical cohort, suggesting reduced time-domain and non-linear HRV measurements in severe OSA compared to other AHI groups. Moreover, their findings demonstrated that OSA seems to play a significant role in obese patients, showing a shift to sympathetic predominance only in obese patients with more severe OSA with increased LF and higher LF/HF compared to obese patients without OSA. There are also hints that OSA therapy normalizes autonomic balance not only during sleep but also at daytime. Glos et al. (84) found that both continuous positive airway pressure (CPAP) as well as mandibular advancement therapy (MAD) therapy led to increased vagal output to the heart, indicated by increased HRV HF components calculated from 5-min short-time recordings under conditions of controlled breathing at daytime.

INFLUENCE OF SLEEP APNEA ON HRV DURING SLEEP

The normalizing effect of OSA therapy on HRV during sleep has also been suggested. Earlier studies report higher sympathetic activity during wake and sleep, but this has normalized, perhaps because of CPAP (73, 85). This is supported by Noda et al.'s (86) study reporting that managed OSA and better sleep quality was associated with a decreased LF. Since then, Abdullah et al. (75) reported an increase in LF and LF/HF in Stages 2 and 3 in sleep apnea compared with healthy patients. This corresponds with results from Dingli et al. (56) and Jurysta et al. (87), which showed an increase in sympathetic and decrease in parasympathetic activity during NREM apnea episodes. Bonnet and Arand (67) reported EEG arousal during Stage 2 and associated HRV changes. Palma et al. reported OSA with hypoxia patients had increased LF and LF/HF during N1 and N2 and REM compared to OSA without hypoxia patients and controls. They also reported that OSA with and without hypoxia had lower HF during NREM and REM in compared to controls (88). In contrast, Jurysta et al. reported no changes in LF/HF and RRI between healthy and OSA subjects. They did however suggest that sympathetic and vagal surges during apneic episodes may suppress the normal shifts between stages of sleep (76). Trimer et al. reported higher LF and LF/HF in moderate OSA subjects compared to normal subjects. Mild OSA subjects also failed to show the linear HRV difference between sleep stages present in non-OSA subjects (20). Kesek et al. studied the relationship between OSA severity and HRV in 387 women and found that high AHI was associated with low variation of sympathetic activity between REM and NREM, suggesting a depressed sympathetic drive and a disability increasing it during REM. These results differ from others, but the study was in healthy women only and gender differences in HRV have been reported (89). Reynolds et al. found a positive correlation between apnea severity and LF in wakefulness and REM sleep, but LF was lower in those with a higher BMI during REM sleep in 105 OSA patients. The suggestion is thus that there is possible autonomic dysfunction in obese apnea patients (90). On the contrary, Oh et al. (91) conducted a 27-participant study and concluded that OSA during REM sleep is not a major contributor of autonomic dysfunction. However, the study was conducted on a small cohort and requires repeated testing to confirm results. In addition, Lado et al. (92) found significant differences in spectral HRV in all three types of intervals (normal breathing, borderline episodes, and sleep apnea) among non-OSA control, mild, and severe OSA subjects during sleep, suggesting that patients with OSA have reduced HRV during sleep even without the presence of sleep apnea (**Figure 1**). In addition, Szollosi et al. (58) compared HRV patterns between OSA and central sleep apnea (CSA), finding higher very low frequency (VLF) percentage, lower LF percentage and HF percentage in CSA, while no significant changes during normal breathings between patients with OSA and CSA. Their results suggested that CSA and OSA have different autonomic modulation, respectively. Overall, the research presented shows increased sympathetic activity during apneic sleep with episodic surges in comparison to healthy sleep, reflected *via* increased LF and LF/HF parameters in HRV.

In seeing the relation of parameters to apneic sleep, there appears to be potential in using HRV as a cost-effective tool for the detection of apnea. Some studies report that cardiac changes visibly precede EEG changes with a range of 10 beats to 5 min in apneic episodes (67, 76). Penzel et al. (93) reported that it was possible to classify apnea *via* HRV with 100% accuracy when comparing to normal subjects and 90% when comparing normal and apneic minute intervals in 35 samples. Roche et al. (94) reached sensitivities of 83 and 89.7% and specificities of 98.1 and 96.5% when using SDNN as a marker in the detection of

FIGURE 1 | Depicts an example of the changes in beat-to-beat intervals (BBI) in an obstructive sleep apnea (OSA) subject with **(upper)** and without **(middle)** the presence of apneic events and a healthy subject **(bottom)** during stage 3 sleep in the supine position.

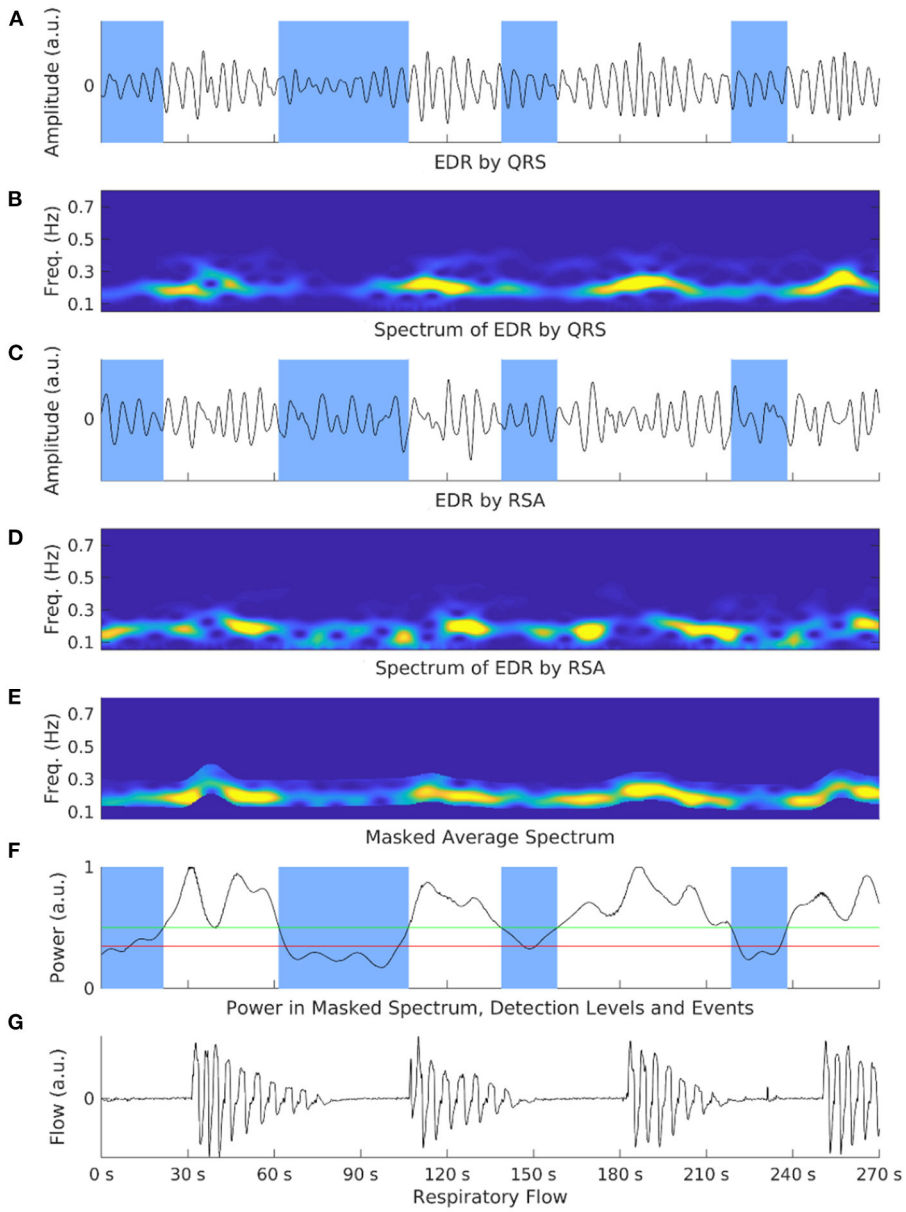

FIGURE 2 | Shows an exemplary illustration of the respiratory power index (RPI) and electrocardiograph-derived respiration (EDR) methods in an OSA patient. Overnight electrocardiograph recordings are processed and cut into limited time segments. EDR signals are calculated *via* ECG respiration embeddings such as QRS complex **(A)** or respiratory sinus arrhythmia (RSA) **(C)**. Spectrograms of both embeddings are also generated **(B,D)**. These spectrograms are normalized and averaged to amplify the respiration-based component and mask non-respiration-related power **(E)**. The power is calculated at each step with two selection events **(F)**. A respiratory flow shows corresponding events to the power spectrum **(G)**. The number of detected apneic events is the RPI.

OSA in groups of 91 and 52 patients, respectively. Then using wavelet decomposition parameters in 147 patients, Roche et al. (95) reached a sensitivity of 92.4% and specificity of 90.1%. Karasulu et al. (96) found a 90.4% sensitivity and 50% specificity when using a VLF cut-off of 9.12, 80 and 76.2% when SDNN was higher than 83 and 73.3 and 85.7% with an SDNN cut-off of 62 in 87 patients. Offering a variant to these results, Abdullah et al. combined EEG and HRV at 64% correct classification accuracy, HRV alone at 56% accuracy and EEG alone at 62% accuracy (75). However, this study was conducted on a small population and thus requires further study in order to improve upon the application to classification. Gil et al. (97) used decreases in amplitude fluctuations of photoplethysmography (PPG) with an accuracy of 80%, sensitivity of 87.5% and specificity of 71.4%. Babaeizadeh and Zhou (98) created a novel method of ECG-derived respiration (EDR) combined with HRV for an accuracy of 88% and correct classification of 71%. Similarly, Lyons et al. (99) developed an ECG-derived respiratory power index (RPI) as

an estimate for AHI to identify severe OSA in commercial drivers (**Figure 2**).

There are thus a variety of tools and combinations that appear to have potential in the detection and classification of apnea.

Collectively this body of studies points to the potential of diagnosing OSA *via* HRV parameters reflecting sympathetic hyperactivity during sleep, particularly during apneic episodes. However, more research needs to be done in this area as there are conflicting reports on the accuracy of using HRV alone, as compared to coordination with other measurements such as EEG, PPG, or EDR. Showing promise in the application of this idea, Le et al. (100) have made wearable device sensor technology predicting apneic episodes 1–5 min before onset with accuracy of 83.6, 80, 76.2, 66.9, and 61.1%, respectively, that could have many applications.

HRV CHANGES DURING AROUSAL

Arousal interrupts sleep continuity to cause sleep fragmentation, which may contribute to cognitive impairment, excessive daytime sleepiness and adverse cardiovascular outcomes in OSA (101–103). Quantification of arousal would improve understanding of the underlying mechanism and relationship between arousal and OSA related outcomes (e.g., daytime sleepiness and functioning) (104, 105). Currently, EEG arousal is defined as the abrupt increase in high-frequency EEG activities lasting 3–15 s, following at least 10 s of sleep during NREM sleep. Additionally, increased chin EMG activity is needed during REM sleep according to the AASM criteria (106, 107). However, even if the concept of arousal should be extended, there currently is no agreement on the classification of arousal (108). Arousal could be divided into several states on the basis of specific causes. Two main types of arousal, physiologic (spontaneous or secondary to various stimuli), and pathologic (induced by sleep hypopnea and apnea, upper airway resistance syndrome or periodic limb movement) are commonly accepted (108, 109). Some studies tried to classify arousal manually based on whether an arousal is associated with a physiological event such as cortical arousal, respiratory arousal, cardiac arousal, movement arousal, snoring arousal, or SpO2 arousal (110, 111). It is reported that autonomic arousal does not have visual recognition in the way EEG arousal does. It is plausible that some peripheral stimulations may not be sufficient to lead to cortical visual EEG arousals but can cause cardiovascular perturbation (e.g., heart rate and blood pressure changes) (112–114).

In this case, autonomic arousal may be a new entity of arousals in OSA during sleep, possibly undetectable by EEG (115). Thirty percent of respiratory event termination causes are still undetermined. Some research indicates that it might be related to apnea-related autonomic arousal, which tends to be ignored due to its non-visible nature compared with other types of arousal in polysomnography (PSG) (116, 117). As a result, PSG would underestimate arousal severity if only visible EEG arousal counts. The occurrence of arousal induced by different causes varies in NREM and REM sleep (116). The underlying mechanisms between the central nervous system (CNS) and autonomic nervous system (ANS) in arousal is poorly understood. Arousal may be a contributor in cardiac alternations such as heart rate changes and blood pressure fluctuation. HRV changes accordingly since heart rate is accelerated and decelerated immediately pre- and post-arousal. Animal studies confirmed that transient arousal from NREM sleep is associated with acute cardiac sympathetic activation and parasympathetic withdrawal (118). The presence of arousal somehow immediately leads to wakefulness that differs in autonomic changes from rested wakefulness in other conditions (118).

Daytime cardiac vagal modulation improves due to the reduction of the frequency of arousals, suggesting arousal may trigger cardiac vagal inhibition. OSA is strongly related to hypertension, which is mainly attributed to sympathetic hyperactivity and/or vagal withdrawal causing a surge in heart rate and blood pressure during apnea-arousal episodes (119, 120). Study of autonomic arousals may help understanding why OSA patients with daytime sleepiness are associated with a higher risk of developing adverse CV outcomes such as hypertension and cardiac sudden death (121). It is reported that patients with co-morbid OSA and insomnia have a significantly higher number of arousals during sleep than OSA alone (122). Bennett et al. (123) found significant correlations between the autonomic arousal index based on pulse transit time analysis and pretreatment objective sleepiness ($r = 0.49$) and nCPAP responsive objective sleepiness ($r = 0.44$), suggesting autonomic arousal detection should be taken into account as a sleep fragmentation index to quantify sleepiness. Bartels et al. tried to define autonomic arousal. They found that lower blood pressure and high heart rate in the 15-s window before short-term cortical arousal and cardiovascular changes shift in the opposite direction after sleep recovery (110).

HRV provides insight to the processing of arousal response during sleep and improves the definition of arousal, criteria of detection and scoring, although it is still controversial. It should be included in the assessment of OSA for its useful clinical value. EEG arousal generally does not cause behavioral awakenings. However, arousal threshold measured by esophageal pressure, a gold standard for upper airway resistance syndrome, is invasive in clinical practice. On the other hand, cardiac arousal may reflect a neural response to stimuli. Little is known about the accumulation of persistent hyperarousal conditions in OSA. HRV would be a sensitive physiological index of autonomic arousal requiring more investigation. Further research is needed to understand the connectivity and interaction between the heart, its intrinsic nervous system, and the brain.

DAYTIME SLEEPINESS AND HRV

On the other end of arousal, daytime sleepiness, a multifactorial psychophysiological state, is one of the predominant symptoms in OSA (124, 125). Currently, the existing findings suggest that daytime sleepiness depends on the quantity and quality of prior sleep. Patients with OSA commonly suffer from reduced sleep quality that is related to fragmented sleep (126). Sleep disturbances caused by arousal are important contributors to

sleepiness (123, 127, 128). Moreover, the frequency of arousal has more impact on sleep recovery than the amount of sleep (129). Subjective and objective sleepiness is often assessed by the Epworth sleepiness scale (ESS) and multiple sleep latency test (MSLT) (130, 131). ESS is a measure of a person's general daytime sleepiness, where a score $\geq$10 could be diagnosed as excessive daytime sleepiness. As a gold standard, the cut-off point of MSLT is still debatable based on the types of patients. According to the AASM, a sleep latency during MSLT of <8 min is defined as sleepiness. However, it is also suggested that mean sleep latency in MSLT <5 min is considered as pathological sleepiness, 5–10 min is suspected sleepiness, and 10–20 min is normal (130).

The prevalence of excessive daytime sleepiness (EDS) in OSA varies from 19 to 87.2% (132–134). However, 50% of individuals with moderate to severe OSA do not report EDS. Lombardi et al. (135) demonstrated that OSA patients with EDS had significantly lower baroreflex sensitivity and significantly higher low-to-high frequency power ratio of HRV during the different stages of nocturnal sleep compared to those without. Furthermore, subjects with EDS have a more blunted parasympathetic and more enhanced sympathetic cardiac drive during all sleep stages suggesting EDS is associated with cardiac autonomic imbalance. Guaita et al. (136) tested whether spectral and non-linear HRV help to differentiate sleep disordered breathing (SDB) patients with and without objective sleepiness, as assessed by the first 3 min of wakefulness during MSLT before sleep onset. Non-linear HRV (Correntropy) failed to detect sleepiness between groups.

However, some studies show that ESS increases with the severity of OSA (2, 137). EDS is not always related to AHI as a number of patients with moderate-to-severe OSA did not report subjective EDS in this evaluation (124, 135, 138). It raised the question of whether ESS is not adequately sensitive to detect sleepiness or if there are other underlying physiopathological mechanisms causing the development of sleepiness in OSA patients. Montemurro et al. (139) found severe OSA without EDS has higher very low frequency-HRV compared to those with EDS, indicating higher sympathetic heart rate control in sleepy patients. However, Sforza et al. (140) found that both diurnal and nocturnal time domain and frequency domain HRV failed to differ sleepy and non-sleepy elderly with unrecognized OSA according to ESS. Time with SaO2 <90% and total autonomic arousals were not significantly different between these two groups. Similarly, Bisogni et al. (141) reported that there is no correlation between EDS assessed by ESS and sympathetic activation in patients with mild to moderate OSA.

HRV AS A RISK MARKER FOR SLEEPINESS RELATED ACCIDENTS

There is little doubt that attentional deficits affect driving capacity. Detection of drowsiness is importance in order to prevent road accidents due to SDB related sleepiness (142). Chua et al. (143) suggested that HRV has a strong association with psychomotor performance measured by psychomotor vigilance tests (PVT) to quantify vigilance performance in drivers. It is in line with previous studies using HRV in machine learning models to predict hypersomnolence in drivers with 90% accuracy (144–146).

It has been shown that sleepy OSA patients have a higher prevalence of adverse cardiovascular outcomes (e.g., hypertension) than non-sleepy OSA patients (147). Furthermore, excessively sleepy OSA patients are at increased risk of incident cardiovascular disease (CVD) compared to other OSA symptom subtypes (Disturbed Sleep, Minimally Symptomatic, and Moderately Sleepy) (121). However, ESS might not be reliable to evaluate the relationship between sleepiness and cardiovascular risk, a surrogate marker of sympathetic activity. MSLT is too time-consuming and costly to be a screening tool to score EDS. Given the association between sleepy OSA and cardiovascular disease has not been established, improving discrimination of sleepiness in OSA patients and the relationship between the severity of daytime sleepiness and HRV in larger-scale studies is required.

Previous studies have proven that CPAP could reduce daytime sleepiness (148). Less benefit from CPAP was found in OSA patients without symptoms than those with, suggesting treatments should be tailored (149–151). There are still 13% of patients with residual EDS after optimal CPAP treatment (152). They also found that the prevalence of residual excessive sleepiness was higher in moderate OSA than severe OSA, suggesting there is an underlying determinant contributing to EDS other than the severity of intermittent hypoxia and AHI. One of the possible determinants could be autonomic dysfunction during sleep. Abnormal autonomic regulation is also known to have an association with higher cardiovascular events in OSA. A possible relation between EDS and cardiovascular events in patients with OSA should be investigated in future studies (i.e., how autonomic dysfunction relates to the presence of EDS and contributes to its relevant consequences in these population).

HRV CHANGES DUE TO HYPOXIA

Exposure to hypoxia is a leading cause of oxidative stress, inflammation, and sympathetic hyperactivity (153). Recurrent oxygen desaturation induced by sleep apnea, one of the distinct features of OSA differing from non-OSA, may be associated with elevated sympathetic nervous activity and blood pressure (153). Additionally, Watson et al. (154) found that the severity of hypoxia is related to graded autonomic dysfunction. Both animal and human experiments demonstrated that the failure to restore cardiovascular adjustment capacity can be ascribed to impaired nerves and blunt responses of the autonomic system as a result of intermittent hypoxemia in OSA (155, 156). A systematic review shows that either SpO2 or SaO2 used to assess arterial oxygen saturation is correlated with time-frequency HRV during hypoxia in normal people at rest (157). Botek et al. (158) found lower arterial oxygen saturation (SpO2) in significantly reduced vagal withdrawal (Ln HF) and increased sympathetic-vagal balance, suggesting SpO2 level is related to the reaction of autonomic control to hypoxia. Their aim was to investigate if HRV could be used as a predictor of SpO2 response to hypoxic challenges

in subjects normoxic at rest. Nevertheless, it is admitted that changes in detailed HRV parameters are not consistently similar due to the varying experimental protocols (e.g., the duration, severity, and types of hypoxia).

OSA generally generates a decrease in HRV during normobaric hypoxia in most reported investigations. However, there are still underlying complex central-peripheral interactions and modulation pathways in vulnerable populations. To address those issues, a growing body of studies have attempted to investigate the hypoxia burden in OSA (159–161). Time-dependent static and dynamic desaturation give more insight to the severity of hypoxia. Acute and chronic hypoxia may lead to different autonomic modulation mechanisms. Hypoxia activated chemoreflex leads to acutely increased short-term sympathetic tone during the occurrence of sleep apnea (54). Furthermore, hypoxia exerted long-lasting chronic effects during the daytime and impaired baroreflex sensitivity (162). Meanwhile whether or not sympathetic hyperactivity induces parasympathetic inhibition is still controversial. The overall reduced HRV with increased sympathetic tone resulted from chronic hypoxia, while a rise in HRV with decreased vagal withdrawal occurred due to the subsequent adaptation and improved tolerance to short-term exposure to repeated hypoxic stress (163). Geovanini et al. demonstrated a vicious circle between hypoxia-induced inflammation and cardiac autonomic abnormality with elevated sympathetic or reduced parasympathetic tone. They also found the values of SDNN, LF, and HF are closely linked to OSA severity while only mean heart rate significantly correlated with augments in neutrophils (164). In an OSA children study, Walter et al. (165) found that OSA may have negative influence on cerebral blood flow due to the attenuated central autonomic control by mediating HRV. Therefore, it is reasonable to believe that different cardiac autonomic modulation responses occur either due to reduced vagal modulation, sympathetic predominance, or even a combination of these responses.

The possibility of an increasing risk in the mortality and morbidity in hypoxic OSA patients with autonomic dysfunction requires further evidence. In addition, both hypoxia and arousal have confounding effects on respiratory-cardiac coupling. Which one is the determinant of cardiac autonomic dysfunction in OSA is controversial in animal and human studies (5). It seems that in prospective animal studies, OSA-induced hypoxia has a persistent impact on daytime hypertension compared to acoustic arousal-induced control models, which exerted nocturnal elevations in blood pressure. However, in humans, the answer to that question is uncertain. Norman et al. suggested that CPAP therapy, which reduced both the intermittent hypoxia and arousals, plays a more important role in improving cardiovascular autonomic function than elimination of nighttime intermittent hypoxia by comparing the results of 24-h ambulatory blood pressure in moderate-to-severe OSA patients who received either CPAP therapy or sham-CPAP with supplemental oxygen (166).

Some studies indicated that certain damages of autonomic function are reversible after eliminating physiological influences (e.g., arousal, hypoxia, and respiratory events) in OSA population with CPAP treatment (81, 167, 168). Thus, HRV maybe become a potential early indicator of the adverse effects of hypoxia on OSA and identifying treatment responses. To date, the effect of nocturnal hypoxia on HRV patterns is unknown and correlation studies of HRV and hypoxia in HRV are limited. Those results may contribute to monitoring the progress of chronic sustained normobaric hypoxia on the cardiovascular and autonomic systems.

HRV IN PEDIATRIC OSA

OSA affects 0.1–13% of children, particularly occurred in pre-school age (169). Pediatric OSA characterize by prolonged partial OSA, which usually occurred in REM sleep, preserved sleep architecture, uncommon OSA-related cortical arousals and recurrent hypoxia (170). Enlarged tonsils and adenoids are the leading causes of OSA in children. Unlike adult OSA manifested with excessive daytime sleepiness and cognitive dysfunction, pediatric OSA is more likely to have negative impact on the development of the central nervous system and cardiovascular system, potentially leading to neurobehavioral deficits (e.g., growth impairment, behavioral, and learning problems) (171). Overt cardiovascular disease is not common in pediatric OSA compared to adults (172), but early evidence shows that pediatric OSA is related to left ventricular hypertrophy (173, 174), abnormal blood pressure fluctuation (175, 176), and reduced systolic and diastolic function (177, 178). HRV analysis is increasingly explored in assessment for cardiovascular autonomic control, the screening and diagnosis of sleep apnea and efficacy of treatments in pediatric OSA during daytime and nighttime due to its feasibility (179, 180). Current findings suggested that altered HRV patterns during daytime and sleep are also found in childhood OSA (181). Not surprising, there are more discrepancies in the results of frequency domain analysis than in time domain analysis due to diverse subject samples and the different methodologies (182, 183). Chaicharn et al. (179) tried to quantify daytime autonomic function in non-OSA and OSA children with spectral HRV analysis, showing OSA children have significant elevated sympathetic tone but normal parasympathetic control, with less reactive response to autonomic tests compared to controls. Liao et al. (182) found autonomic imbalance with increased LF/HF during sleep among groups with different levels of AHI. Similarly, Baharav et al. (183) were able to show sympathetic augmentation with increased LF both during wake before sleep onset and during sleep. By contrast, Kwok et al. (180) demonstrated no changes in most of the important time-domain and HRV measures between non-OSA and OSA children using 1-h ECG data. Impaired baroreflex adaptation is also found in OSA as it is associated with a decrease in nighttime baroreflex gain (184). Autonomic activity may play a key role in pharyngeal compliance of childhood OSA (185). Another application of HRV in childhood OSA is to evaluate treatment response. Muzumdar et al. (186) reported that HRV improved with decreased sympathetic and increased vagal tones after adenotonsillectomy in children with OSA, while no changes showed in HRV in moderate-severe pediatric OSA with 1-year non-invasive ventilation (187). The

results of long-term effect of OSA on HRV are debated. Vlahandonis et al. (188) failed to show significant differences in autonomic regulation determined by using HRV analysis among children with habitual snoring, and those with and without OSA regardless of intervention during 4-year follow-up visits. However, Walter et al. (189) found improved HRV in preschool-aged children with resolved OSA, showing decreased LF and HF, while increased HF in those with unresolved OSA during 3-year period. It is noteworthy that age, obesity, sleep stage, and AHI severity are independently correlated with HRV measurements in children (190, 191). Explanations on these results need to be cautious with those confounding factors. Whether or not HRV measures could be the reliable maker of disease severity and risk stratification in children with OSA is still unproven. The clinical implication of cardiac autonomic alternation in pediatric OSA and how it disrupts the maturation of autonomic control and affects the nervous and cardiovascular functioning need further investigation.

EFFECT OF AGE, ETHNICITY AND SEX ON HRV

Previous studies have demonstrated age-, ethnicity-, and sex-specific differences in HRV in the healthy general population and under certain conditions. It is generally accepted there is an inverse association between age and HRV. However, it is unclear whether the effects of OSA on cardiac autonomic modulation in elderly subjects (>60 yr) are different from those in other age groups (young and mid-aged adults). Trimer et al. compared the differences in HRV among the elderly and the young population with and without OSA. They found the elderly with OSA have significantly lower LF/HF ratio only during wakefulness at night than the young with OSA but not during other sleep stages (192). Sforza et al. (140, 193) suggested age may have more devastating effect on HRV in the elderly, which possibly undermines the application of HRV in those population.

Findings on sex and ethnic differences in HRV are less consistent (194). Nonetheless, reduced HRV is related to higher cardiovascular morbidity and mortality, where decreased cardiac vagal control is considered an important contributor. Currently, a majority of studies report females are characterized by higher vagal control assessed by HF-HRV and lower sympathetic control assessed by LF-HRV (194). Furthermore, women exhibit more complex heart rate dynamics (195). Several studies found no difference between men and women in HF-HRV or that men have a higher HRV (196–200). These results contradict previous findings that women are less likely to develop progressively cardiovascular diseases compared to men (201, 202).

In terms of interaction associations between HRV and age, sex, and ethnicity, Liao et al. (203) found changes in autonomic function have close associations with age, ethnicity, and gender in a community-based cohort by spectral analysis of HRV. They found that the sympathetic and parasympathetic tone decrease with increasing age in a general population. White populations have a higher LF, HF, and lower HF/LF than black populations, suggesting that white populations show sympathetic predominance in cardiac regulation. Men have a higher LF, and a lower HF/LF ratio than women. Those results demonstrate white and male populations have higher sympathetic activity, which is considered as a major contributor to cardiovascular diseases (e.g., hypertension). In contrast, Sloan et al. (200) reported that there is a higher standard deviation of RR intervals in white subjects compared to black subjects, and in men compared to women with age between 33 and 47 years old. No ethnicity- and sex- special differences were found in HF-HRV. Comparatively, Choi et al. found significant ethnically related differences and age-related differences (in Caucasian Americans but not in African Americans) in short-term daytime spectral HRV. Young African Americans showed a similar HRV profile to older Caucasian Americans, leading Choi et al. (204) to suggest the presence premature autonomic nervous system aging in young African Americans. A few studies related to those correlates on HRV during sleep are available. Hall et al. suggested that ethnicity is associated with HRV during sleep. They found white women have decreased parasympathetic tone and elevated sympathetic tone during NREM stage 2 and REM sleep compared to their African American and Chinese counterparts after controlling for confounding factors such as recording length and respiratory rate (205). Huang et al. (206) have shown heart rate profiles in a larger cohort of adults without sleep apnea in order to develop heart rate phenotypes regarding sleep physiology. They implied that heart rate dipping and spectral HRV metrics could contribute to sleep phenotyping due to their significant correlations to sleep measures (e.g., sleep stage, total sleep time and sleep quality). Interpreting the clinical relevance between ethnicity, sex, and HRV should be approached with caution due to the plethora of confounding factors, such as physiological, psychological, behavioral, and sociodemographic factors. To date, there is limited data reporting on the influence of age, ethnicity, and sex on HRV in the OSA population. It is unclear which OSA phenotypes are most likely to develop cardiovascular diseases and thus, which patients are most likely to benefit from CPAP or other forms of therapy for OSA (207). Those findings in cardiac heterogeneity might lead to a better understanding of the underlying cardiovascular pathophysiology and cardiovascular risk stratification in patients with OSA. Additionally, it would facilitate the development of effective strategies for treatment decision of OSA according to cardiac phenotypic characterization in order to improve treatment efficacy and predict treatment outcomes.

HRV AND OSA COMORBIDITY WITH PSYCHIATRY DISEASES

Psychophysiological disturbances have significant impacts on the autonomic nervous system (ANS) (3, 208–211). Depression and anxiety are considered as psychosocial risk factors for cardiovascular comorbidity (212). HRV analysis has been used to quantify autonomic dysregulation in insomnia, depression, anxiety, and schizophrenia (208, 211). Epidemiological data has shown that 39–58% of patients with insomnia and 5–63% of patients with depression had accompanying OSA diagnoses

(213–215). Additionally, it was found that co-morbid OSA and insomnia patients are at a higher risk of developing psychiatric disorders such as anxiety and depression than OSA patients without insomnia (122, 216). Interestingly, OSA and insomnia are more likely to show opposing clinical symptoms related to sleepiness and alertness (215). Nevertheless, increased sympathetic activity and depressed parasympathetic activity were exhibited both in OSA and insomnia (25, 217). It is reported that untreated OSA aggravate insomnia in the disturbed sleep cluster due to hyperarousal (218). Augmentation in heart rate and sympathetic tone, which is thought to be essential to the alertness and motivation, may play a key role in the pathophysiology of insomnia (215). However, interaction mechanisms between OSA and insomnia of autonomic control evaluated by HRV measures remain unclear.

Reduced global HRV is consistently reported in depression and anxiety disorders. Specifically, depression is characterized by increased cardiac rhythmicity and reduced heart rate variability during both sleep and wakefulness (219). Moreover, changes in HRV parameters are associated with alternations in symptom severity of depression (220). Saad et al. (219) showed that a sleep heart rate profiling algorithm detecting whether individuals with sleep complaints experience depression has an identification accuracy of 79.9%. Similarly, anxiety disorders displayed significantly lower HRV (221). Recently, two reviews highlighted the wide applications of HRV in mental health and psychiatric disorders (221). Likewise in populations under 18 years old, there was evidence implied that a resting state measure of HF-HRV is associated with depressive symptoms in children and adolescents with depression (222). In combination with functional brain imaging, HRV mediated by the prefrontal cortex may provide evidence of heart-brain network response to stressors and stimuli to maintain homeostasis (9). Unfortunately, co-morbid psychiatric symptoms and disorders in OSA are often ignored or misdiagnosed. Only a paucity of studies has been reported to investigate ANS dysregulation in OSA populations concomitant with psychiatric conditions *via* HRV analysis.

Evidence of autonomic dysfunction in OSA with various psychiatric and psychological disorders deepens the understanding of their psychopathology and physiopathology associated with negative cardiovascular outcomes. Correlation studies of OSA and neuropsychiatric diseases in ANS function assessed by HRV are lacking. Furthermore, it would be challenging to diagnose and treat co-morbid psychiatry disorders and OSA. It is known that the administration of drugs for psychiatric treatment aggravates OSA as it potentially reduces upper airway muscle tone to impair airway stability, decreases ventilatory response to hypoxia, increases arousal threshold leading to prolongation of respiratory events and deteriorates oxygen saturation. It seems that HRV analysis could be highly applicable in the exploration of the cardiovascular and psychopathological implications in psychiatric disorders. Investigations in the overlapping conditions in physiological and psychological aspects in OSA patients who have worse clinical outcomes and treatment response are warranted. Quintana et al. (223) provide guidelines and recommendations to advance heart rate variability research in psychiatry. We expect more perspectives and possible application of HRV in OSA in neuropsychiatric alternations could be discussed in future studies.

HRV AND CARDIOVASCULAR MORTALITY AND MORBIDITY

Due to HRV being a marker of autonomic innervation of the heart, it has been suggested that increased sympathetic activity during sleep due to OSA may be a link to cardiovascular disease (54). Sympathetic dominance during sleep has been shown in those with ischemic heart disease (53), coronary artery disease (CAD) (55) and post-MI (224). Consequently, HRV parameters are markers for adverse CVD prognoses (49, 51, 52).

Several cardiovascular disease studies have reported an increased risk of mortality in relation to altered HRV parameters. Kleiger et al. found that a 24-h SDNN of <50 ms carried a relative risk of mortality 5.3 times higher than an SDNN of over 100 ms. They suggested that increased sympathetic or decreased vagal tone may predispose to VF (51). Zemaityte et al. (53) found that increased LF and decreased HF was related to the degree of deterioration of IHD functional state in overnight HRV analysis. Post-MI there is a lack of NREM vagal activity that is more likely to lead to lethal arrhythmic events and sudden death (224). Kearney et al. (49) reported that those with chronic HF and 10% lower SDNN had a hazard ratio of 1.06. Rich et al. found that EF and decreased HRV were the best predictors of 12-month mortality post-coronary angiography without recent MI. The HRV contribution to mortality was found to be independent of other disease-related variables, and the 12-month mortality was 18 times higher in those with an HRV <50 ms (52). To further this, Mäkikallio et al. (225) found that random elderly patients with altered HRV parameters predicted a 2.5 relative risk of cardiac death and 4.1 for sudden cardiac death. Algra et al. (226) found that low SDNN was correlated with a 2.6-fold risk of sudden death, also adding that low parasympathetic activity is a risk factor for sudden death. The correlation between altered HRV parameters reflective of dysfunctional sympathovagal balance and increased mortality risk is thus well-established in CVD.

Additionally, CVD and OSA have been shown to be linked (227–234). The Sleep AHEAD study found a greater prevalence of stroke at greater AHI but no association between CHD and OSA (235). However, there were very few patients with CHD and thus the concluded relationship is not a representative analysis of an OSA association with coronary heart disease (CHD). Gottlieb et al. (233) found that OSA was a predictor of incident heart failure with an adjusted hazard ratio of 1.13 per 10 unit increase in AHI. In a meta-analysis of 25,760 subjects, Wang et al. (236). found that severe OSA significantly increases CVD risk, stroke and all-cause mortality with relative risks of 1.79, 2.15, and 1.92, respectively. A positive association was found between moderate OSA and CVD but not with mild OSA. A 10 unit increase in AHI was associated with 17% greater risk of CVD. No correlation was found between CHD and OSA, but again the number of prospective studies relating CHD and OSA were limited and

lacked power for definitive conclusion (236). Yaggi et al. (232) found that OSA independently increases risk of stroke and all-cause mortality with a hazard ratio of 1.97 post-adjustment. In a systematic review, Lavie (234) also concluded that sleep apnea is a mortality risk that can be reduced *via* CPAP, which is especially crucial in younger patients, as they carry a higher mortality risk.

In the linking of OSA and CVD, HRV, and OSA mortality and mortality, the exact physiological pathway through which these are connected is not well-understood. In animal models, Iturriaga (237) proposed that intermittent hypoxia induces carotid body potentiation, and that current evidence indicated that this alters the sympathetic, vascular, and ventilatory response to hypoxia. Whether this is the exact mechanism and whether it increases CVD risk is not definitively known. However, repetitive oxygen desaturation episodes are associated with HRV parameters suggestive of cardiac sympathetic predominance. In a group of CAD patients, those with LVEF >50% had a higher LF:HF ratio than those with LVEF ≤35% during cyclic oxygen desaturation episodes but not during control episodes (55). This suggests that hypoxia worsens pre-existing cardiovascular conditions. A few results of the secondary analyses using ECG data from the Sleep Heart Health Study (SHHS) or the Wisconsin Sleep Cohort Study are reported. Bradicich et al. (238) and Wang et al. (24) demonstrated associations between HRV and characteristics of polysomnographic parameters, however, they did not attempt to use HRV as a CVD risk predictor in this part of the SHHS dataset. Sankari et al. (239) suggested beat-to-beat intervals index (RRDI) during sleep is closely correlated to new-diagnosis CVD (hazard ratio of 1.21 per 10-unit increment in RRDI) in OSA patients from the Wisconsin Sleep Cohort, but they did not utilize other linear and non-linear HRV measures to show the further relationship between CV risk and OSA.

However, despite the clear association between OSA and mortality and CVD, more studies need to be done to determine the exact physiological mechanisms by which this occurs, and if OSA is an independent causal factor of increased mortality and CVD risk as suggested. From the current data, altered HRV features such as SDNN are good predictors of cardiovascular mortality. There appears to be a correlation of higher mortality risk and lower SDNN, but the cut-off point varies depending on the populations and the length of ECG segments. Therefore, determination of a clear cut-off value of SDNN requires further investigation (240).

CONCLUSION

With more sophisticated analytical approaches and techniques developing, HRV measures could provide additional electrophysiological information on impaired cardiovascular alternation, which might be related to subclinical cardiovascular outcomes in patients with OSA. It is already known that the determination of time window (ECG segment length and SDB-related events) is critical to HRV analysis, but a standardized analytical approach is lacking. HRV is proving to be accurate in sleep staging and particularly screening and diagnosing OSA. However, a combinatorial method of HRV and EDR provides hidden information on cardiopulmonary coupling, which transfers from heart rate to respiration and improves the accuracy of sleep apnea detection compared to either method alone. The cognitive consequences and the daytime outcomes of ANS alternation during sleep in patients with OSA are unclear. The use of HRV in the prognosis of OSA independent of CVD is also unclear. However, HRV has shown a close association to mortality and co-morbidities. Additionally, overlapping conditions increase progressively in OSA, requiring reliable tools to manage those conditions at an early stage. Further studies are required to explore the implications of integrated cardiac physiology in regulatory networks between the central brain and heart. In particular, following this investigation, several research topics have been found to be of value:

- Prospective studies using HRV to accurately predict cardiovascular outcomes in OSA should be as a priority for clinical application of HRV research
- Studies investigating cardiac OSA phenotypes on the basis of HRV profiles to facilitate the definition of OSA subtypes and implement tailored treatment approaches in clinical practice
- New sophisticated methods of HRV analysis to analyze the inevitable instationarities of OSA's transitional nature that prove challenging for current algorithms and models
- Context-dependent analyses of HRV (i.e., age, BMI, gender, sleep stages) to better understand the association between anthropometric and sleep characteristics and autonomic function in OSA
- Investigation and standardization of the time window segments analyzed to provide comparable and valuable ECG data in OSA during an overnight sleep study

HRV is showing promise in clinical application and due to the already large and increasing prevalence of OSA, these further studies are imperative to the advancement of diagnostic and treatment approaches needed to minimize the existing and future health and financial burden.

AUTHOR CONTRIBUTIONS

HQ and TP were responsible for the manuscript concept and design. HQ, NS, and TP prepared the manuscript draft. JFK prepared the figures. HQ, NS, TP, MG, NW, JFK, and FV-V contributed to critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité-Universitätsmedizin Berlin.

ACKNOWLEDGMENTS

We appreciate Dr. Mike Mutschelknaus for the editing of the manuscript and HQ is a mentee of World Sleep Society's International Sleep Research Training Program (ISRTP) 2020.

REFERENCES

1. McNicholas WT, Bonsigore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur Respir J.* (2007) 29:156–78. doi: 10.1183/09031936.50027406
2. Bilyukov RG, Nikolov MS, Pencheva VP, Petrova DS, Georgiev OB, Mondeshki TL, et al. Cognitive impairment and affective disorders in patients with obstructive sleep apnea syndrome. *Front Psychiatry.* (2018) 9:357. doi: 10.3389/fpsyt.2018.00357
3. Alvares GA, Quintana DS, Hickie IB, Guastella AJ. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: a systematic review and meta-analysis. *J Psychiatry Neurosci.* (2016) 41:89–104. doi: 10.1503/jpn.140217
4. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* (2019) 7:687–98. doi: 10.1016/S2213-2600(19)30198-5
5. Khoo MC, Blasi A. Sleep-related changes in autonomic control in obstructive sleep apnea: a model-based perspective. *Respir Physiol Neurobiol.* (2013) 188:267–76. doi: 10.1016/j.resp.2013.05.017
6. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* (1996) 93:1043–65.
7. Mazzotti DR, Lim DC, Sutherland K, Bittencourt L, Mindel JW, Magalang U, et al. Opportunities for utilizing polysomnography signals to characterize obstructive sleep apnea subtypes and severity. *Physiol Meas.* (2018) 39:09tr01. doi: 10.1088/1361-6579/aad5fe
8. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord.* (2000) 61:201–16. doi: 10.1016/S0165-0327(00)00338-4
9. Chouchou F, Desseilles M. Heart rate variability: a tool to explore the sleeping brain? *Front Neurosci.* (2014) 8:402. doi: 10.3389/fnins.2014.00402
10. Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri HV, Peng CK, et al. Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace.* (2015) 17:1341–53. doi: 10.1093/europace/euv015
11. Hillebrand S, Gast KB, de Mutsert R, Swenne CA, Jukema JW, Middeldorp S, et al. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *Europace.* (2013) 15:742–9. doi: 10.1093/europace/eus341
12. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science.* (1981) 213:220–2. doi: 10.1126/science.6166045
13. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol.* (1985) 249:H867–75. doi: 10.1152/ajpheart.1985.249.4.H867
14. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput.* (2006) 44:1031–51. doi: 10.1007/s11517-006-0119-0
15. Parati G, Di Rienzo M, Bonsignore MR, Insalaco G, Marrone O, Castiglioni P, et al. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. *J Hypertens.* (1997) 15:1621–6. doi: 10.1097/00004872-199715120-00063
16. Wessel N, Berg K, Kraemer JF, Gapelyuk A, Rietsch K, Hauser T, et al. Cardiac autonomic dysfunction and incidence of *de novo* atrial fibrillation: heart rate variability vs. heart rate complexity. *Front Physiol.* (2020) 11:1583. doi: 10.3389/fphys.2020.596844
17. Seely AJE, Macklem PT. Complex systems and the technology of variability analysis. *Critical Care.* (2004) 8:R367. doi: 10.1186/cc2948
18. Stein PK, Reddy A. Non-linear heart rate variability and risk stratification in cardiovascular disease. *Indian Pacing Electrophys J.* (2005) 5:210–20.
19. Al-Angari HM, Sahakian AV. Use of sample entropy approach to study heart rate variability in obstructive sleep apnea syndrome. *IEEE Trans Biomed Eng.* (2007) 54:1900–4. doi: 10.1109/TBME.2006.889772
20. Trimer R, Mendes RG, Costa FS, Sampaio LM, Delfino A Jr, Arena R, et al. Is there a chronic sleep stage-dependent linear and nonlinear cardiac autonomic impairment in obstructive sleep apnea? *Sleep Breath.* (2014) 18:403–9. doi: 10.1007/s11325-013-0900-x
21. Wessel N, Malberg H, Bauernschmitt R, Kurths J. Nonlinear methods of cardiovascular physics and their clinical applicability. *Int J Bifurcation Chaos.* (2007) 17:3325–71. doi: 10.1142/S0218127407019093
22. Bonnet MH, Arand DL. Heart rate variability: sleep stage, time of night, arousal influences. *Electroencephalogr Clin Neurophysiol.* (1997) 102:390–6. doi: 10.1016/S0921-884X(96)96070-1
23. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* (2010) 90:47–112. doi: 10.1152/physrev.00043.2008
24. Wang W, Tretriluxana S, Redline S, Surovec S, Gottlieb DJ, Khoo MC. Association of cardiac autonomic function measures with severity of sleep-disordered breathing in a community-based sample. *J Sleep Res.* (2008) 17:251–62. doi: 10.1111/j.1365-2869.2008.00652.x
25. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation.* (1998) 98:1071–7. doi: 10.1161/01.CIR.98.11.1071
26. Aydin M, Altin R, Ozeren A, Kart L, Bilge M, Unalacak M. Cardiac autonomic activity in obstructive sleep apnea: time-dependent and spectral analysis of heart rate variability using 24-hour Holter electrocardiograms. *Tex Heart Inst J.* (2004) 31:132–6.
27. Gates GJ, Mateika SE, Basner RC, Mateika JH. Baroreflex sensitivity in nonapneic snorers and control subjects before and after nasal continuous positive airway pressure. *Chest.* (2004) 126:801–7. doi: 10.1378/chest.126.3.801
28. Idiaquez J, Santos I, Santin J, Del Rio R, Iturriaga R. Neurobehavioral and autonomic alterations in adults with obstructive sleep apnea. *Sleep Med.* (2014) 15:1319–23. doi: 10.1016/j.sleep.2014.05.030
29. Müller A, Riedl M, Penzel T, Bonnemeier H, Kurths J, Wessel N. Coupling analysis of transient cardiovascular dynamics. *Biomed Tech.* (2013) 58:131–9. doi: 10.1515/bmt-2012-0030
30. Wessel N, Riedl M, Kramer J, Muller A, Penzel T, Kurths J. Synchronisation and coupling analysis: applied cardiovascular physics in sleep medicine. *Annu Int Conf IEEE Eng Med Biol Soc.* (2013) 2013:6567–70. doi: 10.1109/EMBC.2013.6611060
31. Min KB, Min JY, Paek D, Cho SI, Son M. Is 5-minute heart rate variability a useful measure for monitoring the autonomic nervous system of workers? *Int Heart J.* (2008) 49:175–81. doi: 10.1536/ihj.49.175
32. Li K, Rüdiger H, Ziemssen T. Spectral analysis of heart rate variability: time window matters. *Front Neurol.* (2019) 10:545. doi: 10.3389/fneur.2019.00545
33. Ziemssen T, Reimann M, Gasch J, Rüdiger H. Trigonometric regressive spectral analysis: an innovative tool for evaluating the autonomic nervous system. *J Neural Transm.* (2013) 120(Suppl. 1):S27–33. doi: 10.1007/s00702-013-1054-5
34. Dietrich A, Rosmalen JG, Althaus M, van Roon AM, Mulder LJ, Minderaa RB, et al. Reproducibility of heart rate variability and baroreflex sensitivity measurements in children. *Biol Psychol.* (2010) 85:71–8. doi: 10.1016/j.biopsycho.2010.05.005
35. Parati G. Blood pressure variability: its measurement and significance in hypertension. *J Hypertens Suppl.* (2005) 23:S19–25. doi: 10.1097/01.hjh.0000165624.79933.d3
36. Li K, Konofalska U, Akgün K, Reimann M, Rüdiger H, Haase R, et al. Modulation of cardiac autonomic function by fingolimod initiation and predictors for fingolimod induced bradycardia in patients with multiple sclerosis. *Front Neurosci.* (2017) 11:540. doi: 10.3389/fnins.2017.00540
37. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: measurement and clinical utility. *Ann Noninvasive Electrocardiol.* (2005) 10:88–101. doi: 10.1111/j.1542-474X.2005.10101.x
38. Ziemssen T, Gasch J, Ruediger H. Influence of ECG sampling frequency on spectral analysis of RR intervals and baroreflex sensitivity using the EUROBAVAR data set. *J Clin Monit Comput.* (2008) 22:159–68. doi: 10.1007/s10877-008-9117-0
39. Singh B, Bharti N. Software tools for heart rate variability analysis. *Int J Recent Sci Res.* (2015) 6:3501–6.

40. Pichot V, Gaspoz JM, Molliex S, Antoniadis A, Busso T, Roche F, et al. Wavelet transform to quantify heart rate variability and to assess its instantaneous changes. *J Appl Physiol.* (1999) 86:1081–91. doi: 10.1152/jappl.1999.86.3.1081
41. Pola S, Macerata A, Emdin M, Marchesi C. Estimation of the power spectral density in nonstationary cardiovascular time series: assessing the role of the time-frequency representations (TFR). *IEEE Trans Biomed Eng.* (1996) 43:46–59. doi: 10.1109/10.477700
42. Shaffer F, Meehan ZM, Zerr CL. A critical review of ultra-short-term heart rate variability norms research. *Front Neurosci.* (2020) 14:594880. doi: 10.3389/fnins.2020.594880
43. Rottman JN, Steinman RC, Albrecht P, Bigger JT Jr, Rolnitzky LM, Fleiss JL. Efficient estimation of the heart period power spectrum suitable for physiologic or pharmacologic studies. *Am J Cardiol.* (1990) 66:1522–4. doi: 10.1016/0002-9149(90)90551-b
44. Lombardi F, Sandrone G, Spinnler MT, Torzillo D, Lavezzaro GC, Brusca A, et al. Heart rate variability in the early hours of an acute myocardial infarction. *Am J Cardiol.* (1996) 77:1037–44. doi: 10.1016/s0002-9149(96)00127-0
45. Piccirillo G, Munizzi MR, Fimognari FL, Marigliano V. Heart rate variability in hypertensive subjects. *Int J Cardiol.* (1996) 53:291–8. doi: 10.1016/0167-5273(95)02538-3
46. Friedrich C, Rüdiger H, Schmidt C, Herting B, Prieur S, Junghanns S, et al. Baroreflex sensitivity and power spectral analysis during autonomic testing in different extrapyramidal syndromes. *Mov Disord.* (2010) 25:315–24. doi: 10.1002/mds.22844
47. Maetzler W, Karam M, Berger MF, Heger T, Maetzler C, Ruediger H, et al. Time- and frequency-domain parameters of heart rate variability and sympathetic skin response in Parkinson's disease. *J Neural Transm.* (2015) 122:419–25. doi: 10.1007/s00702-014-1276-1
48. Fei L, Statters DJ, Anderson MH, Malik M, Camm AJ. Relationship between short- and long-term measurements of heart rate variability in patients at risk of sudden cardiac death. *Pacing Clin Electrophysiol.* (1994) 17:2194–200. doi: 10.1111/j.1540-8159.1994.tb03825.x
49. Kearney MT, Fox KA, Lee AJ, Brooksby WP, Shah AM, Flapan A, et al. Predicting sudden death in patients with mild to moderate chronic heart failure. *Heart.* (2004) 90:1137–43. doi: 10.1136/hrt.2003.021733
50. Costa O, Lago P, Rocha AP, Carvalho MJ, Freitas A, Freitas J, et al. Heart rate variability in 24-hour Holter recordings. Comparative study between short- and long-term time- and frequency-domain analyses. *J Electrocardiol.* (1994) 27:251–4. doi: 10.1016/s0022-0736(94)80009-x
51. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* (1987) 59:256–62. doi: 10.1016/0002-9149(87)90795-8
52. Rich MW, Saini JS, Kleiger RE, Carney RM, teVelde A, Freedland KE. Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. *Am J Cardiol.* (1988) 62(10 Pt 1):714–7. doi: 10.1016/0002-9149(88)91208-8
53. Zemaityte D, Varoneckas G, Plauska K, Kaukenas J. Components of the heart rhythm power spectrum in wakefulness and individual sleep stages. *Int J Psychophysiol.* (1986) 4:129–41. doi: 10.1016/0167-8760(86)90006-1
54. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest.* (1995) 96:1897–904. doi: 10.1172/JCI118235
55. Keyl C, Lemberger P, Rödig G, Dambacher M, Frey AW. Changes in cardiac autonomic control during nocturnal repetitive oxygen desaturation episodes in patients with coronary artery disease. *J Cardiovasc Risk.* (1996) 3:221–7.
56. Dingli K, Assimakopoulos T, Wraith PK, Fietze I, Witt C, Douglas NJ. Spectral oscillations of RR intervals in sleep apnoea/hypopnoea syndrome patients. *Eur Respir J.* (2003) 22:943–50. doi: 10.1183/09031936.03.00098002
57. Trinder J, Waloszek J, Woods MJ, Jordan AS. Sleep and cardiovascular regulation. *Pflugers Arch.* (2012) 463:161–8. doi: 10.1007/s00424-011-1041-3
58. Szollosi I, Krum H, Kaye D, Naughton MT. Sleep apnea in heart failure increases heart rate variability and sympathetic dominance. *Sleep.* (2007) 30:1509–14. doi: 10.1093/sleep/30.11.1509
59. Gapelyuk A, Riedl M, Suhrbier A, Kraemer JF, Bretthauer G, Malberg H, et al. Cardiovascular regulation in different sleep stages in the obstructive sleep apnea syndrome. *Biomed Tech.* (2011) 56:207–13. doi: 10.1515/BMT.2011.018
60. Voss A, Wessel N, Sander A, Malberg H, Dietz R. Requirements on sampling rate in Holter systems for analysis of heart rate variability. *Clin Sci.* (1996) 91(Suppl.):120–1. doi: 10.1042/cs0910120supp
61. Voss A, Wessel N, Sander A, Malberg H, Dietz R. Influence of low sampling rate on heart rate variability analysis based on non-linear dynamics. *Comput Cardiol.* (1995) 1995:689–92. doi: 10.1109/CIC.1995.482758
62. Mahdiani S, Jeyhani V, Peltokangas M, Vehkaoja A. Is 50 Hz high enough ECG sampling frequency for accurate HRV analysis? *Annu Int Conf IEEE Eng Med Biol Soc.* (2015) 2015:5948–51. doi: 10.1109/EMBC.2015.7319746
63. Köhler BU, Hennig C, Orglmeister R. The principles of software QRS detection. *IEEE Eng Med Biol Mag.* (2002) 21:42–57. doi: 10.1109/51.993193
64. Pan J, Tompkins WJ. A real-time QRS detection algorithm. *IEEE Trans Biomed Eng.* (1985) 32:230–6. doi: 10.1109/TBME.1985.325532
65. Nabil D, Bereksi Reguig F. Ectopic beats detection and correction methods: a review. *Biomed Signal Process Control.* (2015) 18:228–44. doi: 10.1016/j.bspc.2015.01.008
66. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, et al. AASM scoring manual updates for 2017 (version 2.4). *J Clin Sleep Med.* (2017) 13:665–6. doi: 10.5664/jcsm.6576
67. Bonnet MH, Arand DL. Heart rate variability: sleep stage, time of night, and arousal influences. *Electroencephalogr Clin Neurophysiol.* (1997) 102:390–6. doi: 10.1016/s0921-884x(96)96070-1
68. Brandenberger G, Ehrhart J, Piquard F, Simon C. Inverse coupling between ultradian oscillations in delta wave activity and heart rate variability during sleep. *Clin Neurophysiol.* (2001) 112:992–6. doi: 10.1016/s1388-2457(01)00507-7
69. Baharav A, Kotagal S, Gibbons V, Rubin BK, Pratt G, Karin J, et al. Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. *Neurology.* (1995) 45:1183–7. doi: 10.1212/wnl.45.6.1183
70. Vaughn BV, Quint SR, Messenheimer JA, Robertson KR. Heart period variability in sleep. *Electroencephalogr Clin Neurophysiol.* (1995) 94:155–62. doi: 10.1016/0013-4694(94)00270-u
71. Yang CC, Lai CW, Lai HY, Kuo TB. Relationship between electroencephalogram slow-wave magnitude and heart rate variability during sleep in humans. *Neurosci Lett.* (2002) 329:213–6. doi: 10.1016/s0304-3940(02)00661-4
72. Okada H, Iwase S, Mano T, Sugiyama Y, Watanabe T. Changes in muscle sympathetic nerve activity during sleep in humans. *Neurology.* (1991) 41:1961–6. doi: 10.1212/wnl.41.12.1961
73. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med.* (1993) 328:303–7. doi: 10.1056/NEJM199302043280502
74. Ako M, Kawara T, Uchida S, Miyazaki S, Nishihara K, Mukai J, et al. Correlation between electroencephalography and heart rate variability during sleep. *Psychiatry Clin Neurosci.* (2003) 57:59–65. doi: 10.1046/j.1440-1819.2003.01080.x
75. Abdullah H, Maddage NC, Cosic I, Cvetkovic D. Cross-correlation of EEG frequency bands and heart rate variability for sleep apnoea classification. *Med Biol Eng Comput.* (2010) 48:1261–9. doi: 10.1007/s11517-010-0696-9
76. Jurysta F, Lanquart JP, van de Borne P, Migeotte PF, Dumont M, Degaute JP, et al. The link between cardiac autonomic activity and sleep delta power is altered in men with sleep apnea-hypopnea syndrome. *Am J Physiol Regul Integr Comp Physiol.* (2006) 291:R1165–71. doi: 10.1152/ajpregu.00787.2005
77. Köhler D, Schönhofer B. How important is the differentiation between apnea and hypopnea? *Respiration.* (1997) 64 Suppl 1:15–21. doi: 10.1159/000196731
78. Balachandran JS, Bakker JP, Rahangdale S, Yim-Yeh S, Mietus JE, Goldberger AL, et al. Effect of mild, asymptomatic obstructive sleep apnea on daytime heart rate variability and impedance cardiography measurements. *Am J Cardiol.* (2012) 109:140–5. doi: 10.1016/j.amjcard.2011.07.071
79. Hilton MF, Chappell MJ, Bartlett WA, Malhotra A, Beattie JM, Cayton RM. The sleep apnoea/hypopnoea syndrome depresses waking vagal tone independent of sympathetic activation. *Eur Respir J.* (2001) 17:1258–66. doi: 10.1183/09031936.01.00009301

80. Yasuma F, Hayano J. Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? *Chest.* (2004) 125:683–90. doi: 10.1378/chest.125.2.683
81. Khoo MC, Kim TS, Berry RB. Spectral indices of cardiac autonomic function in obstructive sleep apnea. *Sleep.* (1999) 22:443–51. doi: 10.1093/sleep/22.4.443
82. Park DH, Shin CJ, Hong SC, Yu J, Ryu SH, Kim EJ, et al. Correlation between the severity of obstructive sleep apnea and heart rate variability indices. *J Korean Med Sci.* (2008) 23:226–31. doi: 10.3346/jkms.2008.23.2.226
83. Qin H, Keenan BT, Mazzotti DR, Vaquerizo-Villar F, Kraemer JF, Wessel N, et al. Heart rate variability during wakefulness as a marker of obstructive sleep apnea severity. *Sleep*. (2021) 44:zsab018. doi: 10.1093/sleep/zsab018
84. Glos M, Penzel T, Schoebel C, Nitzsche GR, Zimmermann S, Rudolph C, et al. Comparison of effects of OSA treatment by MAD and by CPAP on cardiac autonomic function during daytime. *Sleep Breath.* (2016) 20:635–46. doi: 10.1007/s11325-015-1265-0
85. Shimizu T, Takahashi Y, Kogawa S, Takahashi K, Kanbayashi T, Saito Y, et al. Muscle sympathetic nerve activity during apneic episodes in patients with obstructive sleep apnea syndrome. *Electroencephalogr Clin Neurophysiol.* (1994) 93:345–52. doi: 10.1016/0168-5597(94)90122-8
86. Noda A, Hayano J, Ito N, Miyata S, Yasuma F, Yasuda Y. Very low frequency componenet of heart rate variability as a marker of therapeutic efficacy in patients with obstructive sleep apnea: preliminary study. *J Res Med Sci.* (2019) 24:84. doi: 10.4103/jrms.JRMS_62_18
87. Jurysta F, van de Borne P, Migeotte PF, Dumont M, Lanquart JP, Degaute JP, et al. A study of the dynamic interactions between sleep EEG and heart rate variability in healthy young men. *Clin Neurophysiol.* (2003) 114:2146–55. doi: 10.1016/s1388-2457(03)00125-3
88. Palma JA, Iriarte J, Fernandez S, Valencia M, Alegre M, Artieda J, et al. Characterizing the phenotypes of obstructive sleep apnea: clinical, sleep, and autonomic features of obstructive sleep apnea with and without hypoxia. *Clin Neurophysiol.* (2014) 125:1783–91. doi: 10.1016/j.clinph.2014.01.029
89. Kesek M, Franklin KA, Sahlin C, Lindberg E. Heart rate variability during sleep and sleep apnoea in a population based study of 387 women. *Clin Physiol Funct Imaging.* (2009) 29:309–15. doi: 10.1111/j.1475-097x.2009.00873.x
90. Reynolds EB, Seda G, Ware JC, Vinik AI, Risk MR, Fishback NF. Autonomic function in sleep apnea patients: increased heart rate variability except during REM sleep in obese patients. *Sleep Breath*. (2007) 11:53–60. doi: 10.1007/s11325-006-0083-9
91. Oh SM, Choi SH, Kim HJ, Park KS, Lee Y. The association between obstructive sleep apnea during REm sleep and autonomic dysfunction as measured by heart rate variability. *Sleep Breath.* (2019) 23:865–71. doi: 10.1007/s11325-018-01799-y
92. Lado MJ, Méndez AJ, Rodríguez-Liñares L, Otero A, Vila XA. Nocturnal evolution of heart rate variability indices in sleep apnea. *Comput Biol Med.* (2012) 42:1179–85. doi: 10.1016/j.compbiomed.2012.09.009
93. Penzel T, McNames J, Murray A, de Chazal P, Moody G, Raymond B. Systematic comparison of different algorithms for apnoea detection based on electrocardiogram recordings. *Med Biol Eng Comput*. (2002) 40:402–7. doi: 10.1007/BF02345072
94. Roche F, Gaspoz JM, Court-Fortune I, Minini P, Pichot V, Duverney D, et al. Screening of obstructive sleep apnea syndrome by heart rate variability analysis. *Circulation*. (1999) 100:1411–15. doi: 10.1161/01.CIR.1001.13.1411
95. Roche F, Pichot V, Sforza E, Court-Fortune I, Duverney D, Costes F, et al. Predicting sleep apnoea syndrome from heart period: a time-frequency wavelet analysis. *Eur Respir J.* (2003) 22:937–42. doi: 10.1183/09031936.03.00104902
96. Karasulu L, Dalar L, Sökücü S, Altin S. Heart rate variability analysis of single-channel electrocardiogram can help to differentiate high-risk patients with obstructive sleep apnea syndrome - a study on diagnostic accuracy. *Anatol J Cardiol.* (2012) 12:331–8. doi: 10.512/akd.2012.097
97. Gil E, Mendez M, Vergara JM, Cerutti S, Bianchi AM, Laguna P. Discrimination of sleep-apnea-related decreases in the amplitude fluctuations of PPG signal in children by HRV analysis. *IEEE Trans Biomed Eng.* (2009) 56:1005–14. doi: 10.1109/TBME.2008.2009340
98. Babaeizadeh S, Zhou SH, Pittman SD, White DP. Electrocardiogram-derived respiration in screening of sleep-disordered breathing. *J Electrocardiol.* (2011) 44:700–6. doi: 10.1016/j.electrocard.2011.08.004
99. Lyons MM, Kraemer JF, Dhingra R, Keenan BT, Wessel N, Glos M, et al. Screening for obstructive sleep apnea in commercial drivers using EKG-derived respiratory power index. *J Clin Sleep Med.* (2019) 15:23–32. doi: 10.5664/jcsm.7562
100. Le T, Bukkapatnam ST. Nonlinear dynamics forecasting of obstructive sleep apnea onsets. *PLoS ONE.* (2016) 12:e0183422. doi: 10.1371/journal.pone.0183422
101. Douglas NJ, Polo O. Pathogenesis of obstructive sleep apnoea/hypopnoea syndrome. *Lancet.* (1994) 344:653–5. doi: 10.1016/S0140-6736(94)92088-5
102. Greenberg GD, Watson RK, Deptula D. Neuropsychological dysfunction in sleep apnea. *Sleep.* (1987) 10:254–62. doi: 10.1093/sleep/10.3.254
103. Roehrs T, Merlotti L, Petrucelli N, Stepanski E, Roth T. Experimental sleep fragmentation. *Sleep.* (1994) 17:438–43. doi: 10.1093/sleep/17.5.438
104. Martin SE, Engleman HM, Deary IJ, Douglas NJ. The effect of sleep fragmentation on daytime function. *Am J Respir Crit Care Med.* (1996) 153:1328–32. doi: 10.1164/ajrccm.153.4.8616562
105. Taylor KS, Murai H, Millar PJ, Haruki N, Kimmerly DS, Morris BL, et al. Arousal from sleep and sympathetic excitation during wakefulness. *Hypertension.* (2016) 68:1467–74. doi: 10.1161/HYPERTENSIONAHA.116.08212
106. Iber C, Ancoli-Israel S, Chesson AL, Quan S. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. Westchester, IL: American Academy of Sleep Medicine (2007).
107. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep*. (1992) 15:173–84. doi: 10.1093/sleep/15.2.174
108. Bonnet MH, Doghramji K, Roehrs T, Stepanski EJ, Sheldon SH, Walters AS, et al. The scoring of arousal in sleep: reliability, validity, and alternatives. *J Clin Sleep Med.* (2007) 3:133–45. doi: 10.5664/jcsm.26815
109. Collard P, Dury M, Delguste P, Aubert G, Rodenstein DO. Movement arousals and sleep-related disordered breathing in adults. *Am J Respir Crit Care Med.* (1996) 154:454–9. doi: 10.1164/ajrccm.154.2.8756822
110. Bartels W, Buck D, Glos M, Fietze I, Penzel T. Definition and importance of autonomic arousal in patients with sleep disordered breathing. *Sleep Med Clin.* (2016) 11:435–44. doi: 10.1016/j.jsmc.2016.08.009
111. Shahrbabaki SS, Ahmed B, Penzel T, Cvetkovic D. Blood pressure and cardiovascular parameters during sleep arousals. *Annu Int Conf IEEE Eng Med Biol Soc.* (2017) 2017:2830–3. doi: 10.1109/EMBC.2017.8037446
112. Davies RJ, Belt PJ, Roberts SJ, Ali NJ, Stradling JR. Arterial blood pressure responses to graded transient arousal from sleep in normal humans. *J Appl Physiol.* (1985) 74:1123–30. doi: 10.1152/jappl.1993.74.3.1123
113. Black JE, Guilleminault C, Colrain IM, Carrillo O. Upper airway resistance syndrome. Central electroencephalographic power and changes in breathing effort. *Am J Respir Crit Care Med.* (2000) 162:406–11. doi: 10.1164/ajrccm.162.2.9901026
114. Guilleminault C, Stoohs R. Arousal, increased respiratory efforts, blood pressure and obstructive sleep apnoea. *J Sleep Res.* (1995) 4:117–24. doi: 10.1111/j.1365-2869.1995.tb00200.x
115. Guilleminault C, Abad VC, Philip P, Stoohs R. The effect of CNS activation versus EEG arousal during sleep on heart rate response and daytime tests. *Clin Neurophysiol.* (2006) 117:731–9. doi: 10.1016/j.clinph.2005.08.035
116. Dingli K, Fietze I, Assimakopoulos T, Quispe-Bravo S, Witt C, Douglas NJ. Arousability in sleep apnoea/hypopnoea syndrome patients. *Eur Respir J.* (2002) 20:733–40. doi: 10.1183/09031936.02.00262002
117. Martin SE, Wraith PK, Deary IJ, Douglas NJ. The effect of nonvisible sleep fragmentation on daytime function. *Am J Respir Crit Care Med.* (1997) 155:1596–601. doi: 10.1164/ajrccm.155.5.9154863
118. Horner RL, Brooks D, Kozar LF, Tse S, Phillipson EA. Immediate effects of arousal from sleep on cardiac autonomic outflow in the absence of breathing in dogs. *J Appl Physiol.* (1985) 79:151–62. doi: 10.1152/jappl.1995.79.1.151
119. Salo TM, Jula AM, Piha JS, Kantola IM, Pelttari L, Rauhala E, et al. Comparison of autonomic withdrawal in men with obstructive sleep apnea syndrome, systemic hypertension, neither condition. *Am J Cardiol.* (2000) 85:232–8. doi: 10.1016/S0002-9149(99)00638-4

120. Narkiewicz K, Somers VK. Sympathetic nerve activity in obstructive sleep apnoea. *Acta Physiol Scand.* (2003) 177:385–90. doi: 10.1046/j.1365-201X.2003.01091.x
121. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med.* (2019) 200:493–506. doi: 10.1164/rccm.201808-1509OC
122. Lang CJ, Appleton SL, Vakulin A, McEvoy RD, Wittert GA, Martin SA, et al. Co-morbid OSA and insomnia increases depression prevalence and severity in men. *Respirology.* (2017) 22:1407–15. doi: 10.1111/resp.13064
123. Bennett LS, Langford BA, Stradling JR, Davies RJ. Sleep fragmentation indices as predictors of daytime sleepiness and nCPAP response in obstructive sleep apnea. *Ame J Respir Critical Care Med.* (1998) 158:778–86. doi: 10.1164/ajrccm.158.3.9711033
124. Mediano O, Barceló A, de la Peña M, Gozal D, Agustí A, Barbé F. Daytime sleepiness and polysomnographic variables in sleep apnoea patients. *Eur Respir J.* (2007) 30:110–3. doi: 10.1183/09031936.00009506
125. Kapur VK, Baldwin CM, Resnick HE, Gottlieb DJ, Nieto FJ. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep.* (2005) 28:472–8. doi: 10.1093/sleep/28.4.472
126. Kimoff RJ. Sleep fragmentation in obstructive sleep apnea. *Sleep.* (1996) 19:S61–6. doi: 10.1093/sleep/19.suppl_9.S61
127. Punjabi NM, O'Hearn D J, Neubauer DN, Nieto FJ, Schwartz AR, Smith PL, et al. Modeling hypersomnolence in sleep-disordered breathing. A novel approach using survival analysis. *Am J Respir Crit Care Med.* (1999) 159:1703–9. doi: 10.1164/ajrccm.159.6.9808095
128. Colt HG, Haas H, Rich GB. Hypoxemia vs sleep fragmentation as cause of excessive daytime sleepiness in obstructive sleep apnea. *Chest.* (1991) 100:1542–8. doi: 10.1378/chest.100.6.1542
129. Bonnet MH, Berry RB, Arand DL. Metabolism during normal, fragmented, recovery sleep. *J Appl Physiol.* (1985) 71:1112–8. doi: 10.1152/jappl.1991.71.3.1112
130. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep.* (1986) 9:519–24. doi: 10.1093/sleep/9.4.519
131. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* (1991) 14:540–5. doi: 10.1093/sleep/14.6.540
132. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* (1993) 328:1230–5. doi: 10.1056/NEJM199304293281704
133. Bjorvatn B, Lehmann S, Gulati S, Aurlien H, Pallesen S, Saxvig IW. Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. *Sleep Breath.* (2015) 19:1387–93. doi: 10.1007/s11325-015-1155-5
134. Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. *Sleep Med.* (2004) 5:339–43. doi: 10.1016/j.sleep.2004.01.021
135. Lombardi C, Parati G, Cortelli P, Provini F, Vetrugno R, Plazzi G, et al. Daytime sleepiness and neural cardiac modulation in sleep-related breathing disorders. *J Sleep Res.* (2008) 17:263–70. doi: 10.1111/j.1365-2869.2008.00659.x
136. Guaita M, Melia U, Vallverdú M, Caminal P, Vilaseca I, Montserrat JM, et al. Regularity of cardiac rhythm as a marker of sleepiness in sleep disordered breathing. *PLoS ONE.* (2015) 10:e0122645. doi: 10.1371/journal.pone.0122645
137. Sun Y, Ning Y, Huang L, Lei F, Li Z, Zhou G, et al. Polysomnographic characteristics of daytime sleepiness in obstructive sleep apnea syndrome. *Sleep Breath.* (2012) 16:375–81. doi: 10.1007/s11325-011-0515-z
138. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. *Am J Respir Crit Care Med.* (1999) 159:502–7. doi: 10.1164/ajrccm.159.2.9804051
139. L. Taranto Montemurro, Floras JS, Picton P, Kasai T, Alshaer H, Gabriel JM, et al. Relationship of heart rate variability to sleepiness in patients with obstructive sleep apnea with and without heart failure. *J Clin Sleep Med.* (2014) 10:271–6. doi: 10.5664/jcsm.3526
140. Sforza E, Pichot V, Martin MS, Barthélémy JC, Roche F. Prevalence and determinants of subjective sleepiness in healthy elderly with unrecognized obstructive sleep apnea. *Sleep Med.* (2015) 16:981–6. doi: 10.1016/j.sleep.2015.03.010
141. Bisogni V, Pengo MF, Drakatos P, Maiolino G, Kent B, Rossitto G, et al. Excessive daytime sleepiness does not correlate with sympathetic nervous system activation and arterial stiffening in patients with mild-to-moderate obstructive sleep apnoea: a proof-of-principle study. *Int J Cardiol.* (2017) 236:458–61. doi: 10.1016/j.ijcard.2017.01.149
142. Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. *N Engl J Med.* (1999) 340:847–51. doi: 10.1056/NEJM199903183401104
143. Chua EC, Tan WQ, Yeo SC, Lau P, Lee I, Mien IH, et al. Heart rate variability can be used to estimate sleepiness-related decrements in psychomotor vigilance during total sleep deprivation. *Sleep.* (2012) 35:325–34. doi: 10.5665/sleep.1688
144. Wang J, Han J, Nguyen VT, Guo L, Guo CC. Improving the test-retest reliability of resting state fMRI by removing the impact of sleep. *Front Neurosci.* (2017) 11:249. doi: 10.3389/fnins.2017.00249
145. Lal SK, Craig A. A critical review of the psychophysiology of driver fatigue. *Biol Psychol.* (2001) 55:173–94. doi: 10.1016/S0301-0511(00)00085-5
146. Borghini G, Astolfi L, Vecchiato G, Mattia D, Babiloni F. Measuring neurophysiological signals in aircraft pilots and car drivers for the assessment of mental workload, fatigue and drowsiness. *Neurosci Biobehav Rev.* (2014) 44:58–75. doi: 10.1016/j.neubiorev.2012.10.003
147. Kapur VK, Resnick HE, Gottlieb DJ. Sleep disordered breathing and hypertension: does self-reported sleepiness modify the association? *Sleep.* (2008) 31:1127–32. doi: 10.5665/sleep/31.8.1127
148. Marshall NS, Barnes M, Travier N, Campbell AJ, Pierce RJ, McEvoy RD, et al. Continuous positive airway pressure reduces daytime sleepiness in mild to moderate obstructive sleep apnoea: a meta-analysis. *Thorax.* (2006) 61:430. doi: 10.1136/thx.2005.050583
149. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, et al. Spanish sleep and breathing network, effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA.* (2012) 307:2161–8. doi: 10.1001/jama.2012.4366
150. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet.* (1994) 343:572–5. doi: 10.1016/S0140-6736(94)91522-9
151. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet.* (2002) 359:204–10. doi: 10.1016/S0140-6736(02)07445-7
152. Gasa M, Tamisier R, Launois SH, Sapene M, Martin F, Stach B, et al. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res.* (2013) 22:389–97. doi: 10.1111/jsr.12039
153. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. *Chest.* (2015) 147:266–74. doi: 10.1378/chest.14-0500
154. Watson JP, Nolan J, Elliott MW. Autonomic dysfunction in patients with nocturnal hypoventilation in extrapulmonary restrictive disease. *Eur Respir J.* (1999) 13:1097–102. doi: 10.1034/j.1399-3003.1999.13e26.x
155. Romero D, Jané R. Non-linear HRV analysis to quantify the effects of intermittent hypoxia using an OSA rat model. In: *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC).* Berlin (2019). p. 4994–7.
156. Alcayaga J, Del Rio R, Moya EA, Freire M, Iturriaga R. Effects of vagotomy on cardiovascular and heart rate variability alterations following chronic normobaric hypoxia in adult rabbits. *Biol Res.* (2018) 51:57. doi: 10.1186/s40659-018-0207-2
157. Akselrod S, Barak Y, Ben-Dov Y, Keselbrener L, Baharav A. Estimation of autonomic response based on individually determined time axis. *Auton Neurosci.* (2001) 90:13–23. doi: 10.1016/S1566-0702(01)00262-4

158. Botek M, Krejčí J, De Smet S, Gába A, McKune AJ. Heart rate variability and arterial oxygen saturation response during extreme normobaric hypoxia. *Auton Neurosci.* (2015) 190:40–5. doi: 10.1016/j.autneu.2015.04.001
159. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J.* (2019) 40:1149–57. doi: 10.1093/eurheartj/ehy624
160. Azarbarzin A, Sands SA, Taranto-Montemurro L, Vena D, Sofer T, Kim SW, et al. The sleep apnea-specific hypoxic burden predicts incident heart failure. *Chest.* (2020) 158:739–50. doi: 10.1016/j.chest.2020.03.053
161. Kainulainen S, Töyräs J, Oksenberg A, Korkalainen H, Sefa S, Kulkas A, et al. Severity of desaturations reflects OSA-related daytime sleepiness better than AHI. *J Clin Sleep Med.* (2019) 15:1135–42. doi: 10.5664/jcsm.7806
162. Lombardi C, Pengo MF, Parati G. Obstructive sleep apnea syndrome and autonomic dysfunction. *Auton Neurosci.* (2019) 221:102563. doi: 10.1016/j.autneu.2019.102563
163. Lizamore CA, Kathiravel Y, Elliott J, Hellemans J, Hamlin MJ. The effect of short-term intermittent hypoxic exposure on heart rate variability in a sedentary population. *Physiol Int.* (2016) 103:75–85. doi: 10.1556/036.103.2016.1.7
164. Geovanini GR, Wang R, Weng J, Tracy R, Jenny NS, Goldberger AL, et al. Elevations in neutrophils with obstructive sleep apnea: the Multi-Ethnic Study of Atherosclerosis (MESA). *Int J Cardiol.* (2018) 257:318–23. doi: 10.1016/j.ijcard.2017.10.121
165. Walter LM, Tamanyan K, Weichard AJ, Biggs SN, Davey MJ, Nixon GM, et al. Age and autonomic control, but not cerebral oxygenation, are significant determinants of EEG spectral power in children. *Sleep.* (2019) 42:zsz118. doi: 10.1093/sleep/zsz118
166. Norman D, Loredo JS, Nelesen RA, Ancoli-Israel S, Mills PJ, Ziegler MG, et al. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. *Hypertension.* (2006) 47:840–5. doi: 10.1161/01.HYP.0000217128.41284.78
167. Nicholl DDM, Hanly PJ, Zalucky AA, Mann MC, MacRae JM, Poulin MJ, et al. CPAP therapy delays cardiovagal reactivation and decreases arterial renin-angiotensin system activity in humans with obstructive sleep apnea. *J Clin Sleep Med.* (2018) 14:1509–20. doi: 10.5664/jcsm.7326
168. Khoo MC, Belozeroff V, Berry RB, Sassoon CS. Cardiac autonomic control in obstructive sleep apnea: effects of long-term CPAP therapy. *Am J Respir Crit Care Med.* (2001) 164:807–12. doi: 10.1164/ajrccm.164.5.2010124
169. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. *Proc Am Thoracic Soc.* (2008) 5:242–52. doi: 10.1513/pats.200708-135MG
170. Marcus CL. Sleep-disordered breathing in children. *Am J Respir Crit Care Med.* (2001) 164:16–30. doi: 10.1164/ajrccm.164.1.2008171
171. Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. *Sleep.* (2006) 29:1115–34. doi: 10.1093/sleep/29.9.1115
172. Ehsan Z, Ishman SL, Kimball TR, Zhang N, Zou Y, Amin RS. Longitudinal cardiovascular outcomes of sleep disordered breathing in children: a meta-analysis and systematic review. *Sleep.* (2017) 40:zsx015. doi: 10.1093/sleep/zsx015
173. Amin R, Somers VK, McConnell K, Willging P, Myer C, Sherman M, et al. Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. *Hypertension.* (2008) 51:84–91. doi: 10.1161/HYPERTENSIONAHA.107.099762
174. Amin RS, Kimball TR, Bean JA, Jeffries JL, Willging JP, Cotton RT, et al. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. *Am J Respir Crit Care Med.* (2002) 165:1395–9. doi: 10.1164/rccm.2105118
175. O'Driscoll DM, Foster AM, Ng ML, Yang JS, Bashir F, Nixon GM, et al. Acute cardiovascular changes with obstructive events in children with sleep disordered breathing. *Sleep.* (2009) 32:1265–71. doi: 10.1093/sleep/32.10.1265
176. Leung LC, Ng DK, Lau MW, Chan CH, Kwok KL, Chow PY, et al. Twenty-four-hour ambulatory BP in snoring children with obstructive sleep apnea syndrome. *Chest.* (2006) 130:1009–17. doi: 10.1016/S0012-3692(15)51134-3
177. Kaditis AG, Alexopoulos EI, Dalapascha M, Papageorgiou K, Kostadima E, Kaditis DG, et al. Cardiac systolic function in Greek children with obstructive sleep-disordered breathing. *Sleep Med.* (2010) 11:406–12. doi: 10.1016/j.sleep.2009.05.019
178. Ugur MB, Dogan SM, Sogut A, Uzun L, Cinar F, Altin R, et al. Effect of adenoidectomy and/or tonsillectomy on cardiac functions in children with obstructive sleep apnea. *J Oto-rhino-laryngol Related Specialties.* (2008) 70:202–8. doi: 10.1159/000124295
179. Chaicharn J, Lin Z, Chen ML, Ward SL, Keens T, Khoo MC. Model-based assessment of cardiovascular autonomic control in children with obstructive sleep apnea. *Sleep.* (2009) 32:927–38. doi: 10.1093/sleep/32.7.927
180. Kwok KL, Yung TC, Ng DK, Chan CH, Lau WF, Fu YM. Heart rate variability in childhood obstructive sleep apnea. *Pediatric Pulmonol.* (2011) 46:205–10. doi: 10.1002/ppul.21268
181. Aljadeff G, Gozal D, Schechtman VL, Burrell B, Harper RM, Ward SL. Heart rate variability in children with obstructive sleep apnea. *Sleep.* (1997) 20:151–7. doi: 10.1093/sleep/20.2.151
182. Liao D, Li X, Rodriguez-Colon SM, Liu J, Vgontzas AN, Calhoun S, et al. Sleep-disordered breathing and cardiac autonomic modulation in children. *Sleep Med.* (2010) 11:484–8. doi: 10.1016/j.sleep.2009.11.012
183. Baharav A, Kotagal S, Rubin BK, Pratt J, Akselrod S. Autonomic cardiovascular control in children with obstructive sleep apnea. *Clin Autonomic Res.* (1999) 9:345–51. doi: 10.1007/BF02318382
184. McConnell K, Somers VK, Kimball T, Daniels S, VanDyke R, Fenchel M, et al. Baroreflex gain in children with obstructive sleep apnea. *Am J Respir Crit Care Med.* (2009) 180:42–8. doi: 10.1164/rccm.200808-1324OC
185. Bokov P, Mauvais FX, Madani A, Matrot B, Lecendreux M, Delanoë C, et al. Cross-sectional case-control study of the relationships between pharyngeal compliance and heart rate variability indices in childhood obstructive sleep apnoea. *J Sleep Res.* (2021) e13337. doi: 10.1111/jsr.13337. [Epub ahead of print].
186. Muzumdar HV, Sin S, Nikova M, Gates G, Kim D, Arens R. Changes in heart rate variability after adenotonsillectomy in children with obstructive sleep apnea. *Chest.* (2011) 139:1050–9. doi: 10.1378/chest.10-1555
187. Kirk VG, Edgell H, Joshi H, Constantin E, Katz SL, MacLean JE. Cardiovascular changes in children with obstructive sleep apnea and obesity after treatment with noninvasive ventilation. *J Clin Sleep Med.* (2020) 16:2063–71. doi: 10.5664/jcsm.8760
188. Vlahandonis A, Yiallourou SR, Sands SA, Nixon GM, Davey MJ, Walter LM, et al. Long-term changes in heart rate variability in elementary school-aged children with sleep-disordered breathing. *Sleep Med.* (2014) 15:76–82. doi: 10.1016/j.sleep.2013.06.023
189. Walter LM, Biggs SN, Nisbet LC, Weichard AJ, Hollis SL, Davey MJ, et al. Improved long-term autonomic function following resolution of sleep-disordered breathing in preschool-aged children. *Sleep Breath.* (2016) 20:309–19. doi: 10.1007/s11325-015-1268-x
190. Liao D, Li X, Vgontzas AN, Liu J, Rodriguez-Colon S, Calhoun S, et al. Sleep-disordered breathing in children is associated with impairment of sleep stage-specific shift of cardiac autonomic modulation. *J Sleep Res.* (2010) 19:358–65. doi: 10.1111/j.1365-2869.2009.00807.x
191. Van Eyck, Van Hoorenbeeck K, De Winter BY, Van Gaal L, De Backer W, Verhulst SL. Sleep disordered breathing and autonomic function in overweight and obese children and adolescents. *ERJ Open Res.* (2016) 2:00038–2016. doi: 10.1183/23120541.00038-2016
192. Trimer R, Cabidu R, Sampaio LL, Stirbulov R, Poiares D, Guizilini S, et al. Heart rate variability and cardiorespiratory coupling in obstructive sleep apnea: elderly compared with young. *Sleep Med.* (2014) 15:1324–31. doi: 10.1016/j.sleep.2014.05.028
193. Sforza E, Chouchou F, Pichot V, Barthélémy JC, Roche F. Heart rate increment in the diagnosis of obstructive sleep apnoea in an older population. *Sleep Med.* (2012) 13:21–8. doi: 10.1016/j.sleep.2011.04.011
194. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: a meta-analysis. *Neurosci Biobehav Rev.* (2016) 64:288–310. doi: 10.1016/j.neubiorev.2016.03.007
195. Ryan Sheila M, Goldberger Ary L, Pincus Steven M, Mietus J, Lipsitz Lewis A. Gender- and age-related differences in heart rate dynamics: are women more complex than men? *J Am Coll Cardiol.* (1994) 24:1700–7. doi: 10.1016/0735-1097(94)90177-5
196. Bigger JT, Jr., Fleiss JL, Steinman RC, Rolnitzky LM, Schneider WJ, et al. RR variability in healthy, middle-aged persons compared with patients

with chronic coronary heart disease or recent acute myocardial infarction. *Circulation.* (1995) 91:1936–43. doi: 10.1161/01.CIR.91.7.1936
197. Pikkujämsä SM, Mäkikallio TH, Airaksinen KE, Huikuri HV. Determinants and interindividual variation of R-R interval dynamics in healthy middle-aged subjects. *Am J Physiol Heart Circ Physiol.* (2001) 280:H1400–6. doi: 10.1152/ajpheart.2001.280.3.H1400
198. Lampert R, Ickovics J, Horwitz R, Lee F. Depressed autonomic nervous system function in African Americans and individuals of lower social class: a potential mechanism of race- and class-related disparities in health outcomes. *Am Heart J.* (2005) 150:153–60. doi: 10.1016/j.ahj.2004.08.008
199. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol.* (1998) 31:593–601. doi: 10.1016/S0735-1097(97)00554-8
200. Sloan RP, Huang MH, McCreath H, Sidney S, Liu K, Dale Williams O, et al. Cardiac autonomic control and the effects of age, race, and sex: the CARDIA study. *Auton Neurosci.* (2008) 139:78–85. doi: 10.1016/j.autneu.2008.01.006
201. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation.* (2011) 124:2145–54. doi: 10.1161/CIRCULATIONAHA.110.968792
202. Maas AH, Appelman YE. Gender differences in coronary heart disease. *Neth Heart J.* (2010) 18:598–602. doi: 10.1007/s12471-010-0841-y
203. Liao D, Barnes RW, Chambless LE, Simpson RJ Jr, Sorlie P, Heiss G, et al. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability–the ARIC study. Atherosclerosis risk in communities. *Am J Cardiol.* (1995) 76:906–12. doi: 10.1016/S0002-9149(99)80260-4
204. Choi JB, Hong S, Nelesen R, Bardwell WA, Natarajan L, Schubert C, et al. Age and ethnicitiy differences in short-term heart-rate variability. *Psychosom Med.* (2006) 68:421–26. doi: 10.1097/01.psy.0000221378.09239.6a
205. Hall MH, Middleton K, Thayer JF, Lewis TT, Kline CE, Matthews KA, et al. Racial differences in heart rate variability during sleep in women: the study of women across the nation sleep study. *Psychosom Med.* (2013) 75:783–90. doi: 10.1097/PSY.0b013e3182a7ec5c
206. Huang Z, Goparaju B, Chen H, Bianchi MT. Heart rate phenotypes and clinical correlates in a large cohort of adults without sleep apnea. *Nat Sci Sleep.* (2018) 10:111–125. doi: 10.2147/NSS.S155733
207. Carter JR, Mokhlesi B, Thomas RJ. Obstructive sleep apnea phenotypes and cardiovascular risk: is there a role for heart rate variability in risk stratification? *Sleep*. (2021) 44:zsab037. doi: 10.1093/sleep/zsab037
208. Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. *Am Heart J.* (2000) 140:77–83. doi: 10.1067/mhj.2000.109981
209. Kemp AH, Brunoni AR, Santos IS, Nunes MA, Dantas EM, Carvalho de Figueiredo R, et al. Effects of depression, anxiety, comorbidity, and antidepressants on resting-state heart rate and its variability: an ELSA-Brasil cohort baseline study. *Am J Psychiatry.* (2014) 171:1328–34. doi: 10.1176/appi.ajp.2014.13121605
210. Moon E, Lee SH, Kim DH, Hwang B. Comparative study of heart rate variability in patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, or major depressive disorder. *Clin Psychopharmacol Neurosci.* (2013) 11:137–43. doi: 10.9758/cpn.2013.11.3.137
211. Quintana DS, Westlye LT, Kaufmann T, Rustan ØG, Brandt CL, Haatveit B, et al. Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls. *Acta Psychiatr Scand.* (2016) 133:44–52. doi: 10.1111/acps.12498
212. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PLoS ONE.* (2012) 7:e30777. doi: 10.1371/journal.pone.0030777
213. Benetó A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. *Sleep Med Rev.* (2009) 13:287–93. doi: 10.1016/j.smrv.2008.09.006
214. Ejaz SM, Khawaja IS, Bhatia S, Hurwitz TD. Obstructive sleep apnea and depression: a review. *Innov Clin Neurosci.* (2011) 8:17–25.
215. Luyster FS, Buysse DJ, Strollo PJ Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med.* (2010) 6:196–204. doi: 10.5664/jcsm.27772
216. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation.* (2001) 104:2024–8. doi: 10.1161/hc4201.097834
217. Spiegelhalder K, Fuchs L, Ladwig J, Kyle SD, Nissen C, Voderholzer U, et al. Heart rate and heart rate variability in subjectively reported insomnia. *J Sleep Res.* (2011) 20:137–45. doi: 10.1111/j.1365-2869.2010.00863.x
218. Ye L, Pien GW, Ratcliffe SJ, Björnsdottir E, Arnardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J.* (2014) 44:1600–7. doi: 10.1183/09031936.00032314
219. Saad M, Ray LB, Bujaki B, Parvaresh A, Palamarchuk I, De Koninck J, et al. Using heart rate profiles during sleep as a biomarker of depression. *BMC Psychiatry.* (2019) 19:168. doi: 10.1186/s12888-019-2152-1
220. Hartmann R, Schmidt FM, Sander C, Hegerl U. Heart rate variability as indicator of clinical state in depression. *Front Psychiatry.* (2018) 9:735. doi: 10.3389/fpsyt.2018.00735
221. Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front Psychiatry.* (2014) 5:80. doi: 10.3389/fpsyt.2014.00080
222. Koenig J, Kemp AH, Beauchaine TP, Thayer JF, Kaess M. Depression and resting state heart rate variability in children and adolescents - a systematic review and meta-analysis. *Clin Psychol Rev.* (2016) 46:136–50. doi: 10.1016/j.cpr.2016.04.013
223. Quintana DS, Alvares GA, Heathers JA. Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH): recommendations to advance research communication. *Transl Psychiatry.* (2016) 6:e803. doi: 10.1038/tp.2016.73
224. Vanoli E, Adamson PB, Ba-lin, Pinna GD, Lazarra R, Orr WC. Heart rate variability during specific sleep stages: a comparison of healthy subjects with patients after myocardial infarction. *Circulation*. (1995) 91:1918–22. doi: 10.1161/01.CIR.91.7.1918
225. Mäkikallio TH, Huikuri HV, Mäkikallio A, Sourander LB, Mitrani RD, Castellanos A, et al. Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. *J Am Coll Cardiol.* (2001) 37:1395–402. doi: 10.1016/S0735-1097(01)01171-8
226. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. Heart rate variability from 24-hour electrocardiography and the 2-year risk for sudden death. *Circulation*. (1993) 88:180–5. doi: 10.1161/01.cir.88.1.180
227. Wolk R, Kara T, Somers VK. Sleep-disorder breathing and cardiovascular disease. *Circulation*. (2003) 108:9–12. doi: 10.1161/01.CIR.0000072346.56728.E4
228. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: the Sleep Heart Health Study. *JAMA*. (2000) 283:1829–36. doi: 10.1001/jama.283.14.1829
229. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med.* (2001) 163:19–25. doi: 10.1164/ajrccm.163.1.2001008
230. Yeboah J, Redline S, Johnson C, Tracy R, Ouyang P, Blumenthal RS, et al. Association between sleep apnea, snoring, incident cardiovascular events and all-cause mortality in an adult population: MESA. *Atherosclerosis*. (2011) 219:963–68. doi: 10.1016/j.atherosclerosis.2011.08.021
231. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*. (2008) 118:1080–111. doi: 10.1611/CIRCULATIONAHA.107.189375
232. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med*. (2005) 353:2034–41. doi: 10.1056/NEJMoa043104

233. Gottlieb DK, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. *Circulation*. (2010) 122:352–60. doi: 10.1161/CIRCULATIONAHA.109.901801
234. Lavie P. Mortality in sleep apnoea syndrome: a review of the evidence. *Euro Respir Rev*. (2007) 16:203. doi: 10.1183/09059180.00010610
235. Rice TB, Foster GD, Sanders MH, Unruh M, Reboussin D, Kuna ST, et al. The relationship between obstructive sleep apnea and self-reported stroke or coronary heart disease in overweight and obese adults with type 2 diabetes mellitus. *Sleep*. (2012) 35:1293–8. doi: 10.5665/sleep.2090
236. Wang X, Ouyang Y, Wang Z, Zhao G, Liu L, Bi Y. Obstructive sleep apnea and risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol*. (2013) 169:207–14. doi: 10.1016/j.ijcard.2013.08.088
237. Iturriaga R. Intermittent hypoxia: endothelin-1 and hypoxic carotid body chemosensory potentiation. *Exp Physiol*. (2013) 98:1550–51. doi: 10.1113/expphysiol.2013.075820
238. Bradicich M, Sievi NA, Grewe FA, Gasperetti A, Kohler M, Schwarz EI. Nocturnal heart rate variability in obstructive sleep apnoea: a cross-sectional analysis of the Sleep Heart Health Study. *J Thoracic Dis*. (2020) 12:S129–38. doi: 10.21037/jtd-cus-2020-005
239. Sankari A, Ravelo LA, Maresh S, Aljundi N, Alsabri B, Fawaz S, et al. Longitudinal effect of nocturnal R-R intervals changes on cardiovascular outcome in a community-based cohort. *BMJ Open*. (2019) 9:e030559. doi: 10.1136/bmjopen-2019-030559
240. Singh N, Moneghetti KJ, Christle JW, Hadley D, Froelicher V, Plews D. Heart rate variability: an old metric with new meaning in the Era of using mHealth technologies for health and exercise training guidance. Part two: prognosis and training. *Arrhythm Electrophysiol Rev*. (2018) 7:247–55. doi: 10.15420/aer.2018.30.2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership