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SCIENTIFIC INVESTIGATIONS

Sleep structure in patients with COMISA compared to OSA and insomnia

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Study Objectives: Obstructive sleep apnea (OSA) and insomnia frequently co-occur, making diagnosis and treatment challenging. We investigated differences in sleep structure between patients with OSA, insomnia, and comorbid insomnia and sleep apnea (COMISA) to identify characteristics that can be used to improve the diagnosis of COMISA.

Methods: We obtained polysomnography data of 326 patients from the Sleep and OSA Monitoring with Non-Invasive Applications database. The group included patients with OSA (n = 199), insomnia (n = 47), and COMISA (n = 80). We compared statistics related to sleep structure between the 3 patient groups.

Results: Wake after sleep onset was significantly shorter for the OSA group (median: 60.0 minutes) compared to the COMISA (median: 83.3 minutes, $P < .01$) and the insomnia (median: 83.5 minutes, $P = .01$) groups. No significant differences were found in the total number of awakenings and the number of short (up to and including 2 minutes) and medium-length awakenings (2.5 up to and including 4.5 minutes). However, the number of long awakenings (5 minutes or longer) and wake after sleep onset containing only long awakenings was significantly lower for patients with OSA (median: 2 awakenings and 25.5 minutes) compared to patients with COMISA (median: 3 awakenings, $P < .01$ and 43.3 minutes, $P < .001$) or with insomnia (median: 3 awakenings, $P < .01$ and 56.0 minutes, $P < .001$). Total sleep time was significantly longer and sleep efficiency was significantly higher for the OSA group (median: 418.5 minutes and 84.4%) compared to both the COMISA (median: 391.5 minutes, $P < .001$ and 77.3%, $P < .001$) and the insomnia (median: 381.5 minutes, $P < .001$ and 78.2%, $P < .001$) groups. The number of sleep-stage transitions during the night for patients with COMISA (median: 194.0) was lower compared to that for patients with OSA (median: 218.0, $P < .01$) and higher compared to that for patients with insomnia (median: 156.0, $P < .001$). Other sleep architectural parameters were not discriminative between the groups.

Conclusions: Patients with COMISA show specific characteristics of insomnia, including prolonged awakenings. This variable is distinctive in comparison to patients with OSA. The combination of prolonged awakenings and the presence of sleep-disordered breathing leads to increased sleep disturbance compared to patients having only 1 of the sleep disorders.

Keywords: sleep apnea, insomnia, COMISA, polysomnography, wakefulness, awakenings, sleep structure

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea and insomnia frequently coexist, and diagnosis remains challenging when they do. Research is needed to identify characteristics that can be used to distinguish patients with comorbid insomnia and sleep apnea from patients with obstructive sleep apnea or insomnia. Early diagnosis is beneficial since both sleep disorders can aggravate each other and influence treatment outcome and comorbid insomnia and sleep apnea is associated with increased risk of all-cause mortality.

Study Impact: A detailed analysis of sleep structure showed differences in duration and frequency of awakenings between patients with obstructive sleep apnea, comorbid insomnia and sleep apnea, and insomnia. These characteristics could help improve diagnosis of comorbid insomnia and sleep apnea.

INTRODUCTION

Insomnia and obstructive sleep apnea (OSA) are the most common sleep disorders in the general population. Both disorders are associated with impaired daytime functioning and decreased mental health and quality of life.[1] OSA and insomnia can occur simultaneously in the same patient, a condition called comorbid insomnia and sleep apnea (COMISA). However, it is challenging to diagnose COMISA due to overlapping clinical features between insomnia and OSA, such as frequent awakenings, difficulties falling asleep, and fatigue.[2] The diagnosis of OSA requires a clinical assessment of complaints in combination with a single-night polysomnography (PSG), polygraphy, or home sleep apnea test with a technically adequate device (at least a type III device with a minimum of 4 channels).[3] The diagnosis of insomnia requires a clinical assessment including history taking and the recording of sleep diaries.[4] The combined diagnosis might be missed as a consequence of the different diagnostic procedures. It is known that this comorbid sleep disorder occurs frequently, with studies describing a prevalence of COMISA in the general population[5–8] and in sleep clinic populations,[2,9,10] ranging from 40–60% of patients with OSA having insomnia (symptoms) and 30–65% of patients with insomnia having OSA. However, the exact prevalence of this condition is

difficult to determine due to the variability in the definition of insomnia and OSA in the available studies.

Apart from the likelihood of occurring simultaneously, OSA and insomnia seem to aggravate each other.[2,11] In addition, COMISA is associated with an increased risk of all-cause mortality compared to either insomnia or OSA alone.[12] Various studies have established that COMISA is also related to greater sleep disturbance, impaired daytime functioning, and reduced quality of life compared to either insomnia or OSA alone.[7,13–18] This highlights the importance of early recognition of COMISA and the need for identified characteristics that can be used to distinguish patients with COMISA from patients with OSA or insomnia. Sleep structure could provide information in this regard.

Several studies compared sleep structure based on PSG-derived parameters in patients with OSA, insomnia, or COMISA but yielded inconsistent results. For example, Lichstein et al found no significant differences for wake after sleep onset (WASO) between the 3 patients groups, whereas Bianchi et al reported a significantly longer WASO for COMISA vs OSA and insomnia and 2 other studies demonstrated a longer WASO for COMISA and insomnia compared to OSA.[15,19–21] Inconsistencies between studies could be explained by the different definitions used to determine the presence of insomnia and therefore also COMISA. For example, Lichstein et al and Choi et al included patients with a diagnosis of OSA, insomnia, or COMISA (defined as having both sleep disorders) based on the *International Classification of Sleep Disorders*, second edition (ICSD-2) criteria, whereas other studies defined the presence of insomnia based on self-reported insomnia symptoms.[15,19–21] Despite the disparate findings, these studies suggest the presence of differences in sleep and wake parameters obtained from PSG between patients with OSA, insomnia, or COMISA, hinting that a more detailed analysis of commonly used sleep parameters could yield additional information and may provide diagnostic value.

WASO is an interesting sleep parameter that is often used in sleep research since it provides information about the extent of wakefulness occurring after sleep onset. However, it hides information about the length of awakenings: A long WASO can consist of many short awakenings or a few long awakenings. This could be a relevant difference between OSA and insomnia since patients with OSA can experience frequent, short postobstruction awakenings and insomnia can be characterized by both multiple brief and prolonged nocturnal awakenings.[22,23] The identification of such characteristics may improve recognition of COMISA and may facilitate earlier diagnosis and treatment, likely resulting in improved clinical outcomes.

In this study, we investigate differences in the sleep structure, measured with PSG, between patients with OSA, insomnia, or COMISA. The aim is to identify characteristics that can be used to improve the diagnosis of COMISA. Patients with insomnia or COMISA can obviously be distinguished based on the presence of breathing events, but the main challenge is to differentiate between OSA and COMISA. We hypothesize that the length of awakenings may be a distinctive feature between patients with OSA and those with COMISA.

METHODS

Study participants

We analyzed data from the Sleep and OSA Monitoring with Non-Invasive Applications (SOMNIA) database, which includes a prospective cohort of patients with various sleep disorders from the Sleep Medicine Center Kempenhaeghe (Heeze, The Netherlands), a multidisciplinary expert center for sleep medicine.[24] The SOMNIA database includes unselected patients scheduled for a routine diagnostic PSG and facilitates, among other things, the development of additional indices and biomarkers from traditional sleep monitoring methods.

Given our interest in evaluating sleep structure in patients with OSA, insomnia, and COMISA, we included patients in 3 groups according to their formal clinical diagnosis. Both OSA and insomnia were diagnosed according to the ICSD-2 and later by the Third edition (ICSD-3) criteria by an experienced sleep physician.[1,25] For this study, we recoded the previous ICSD-2 diagnoses according to the ICSD-3 under a single diagnosis of "insomnia disorder." The criteria for a diagnosis of insomnia include difficulties with initiation or maintenance of sleep and associated daytime consequences, despite adequate opportunity and circumstances to sleep, with a duration of at least 3 months and a frequency of at least 3 times per week. All available PSGs that were collected up to September 1, 2020, were included when meeting the following criteria. The OSA group includes patients with a diagnosis of OSA and no sleep disorder other than OSA. The insomnia group includes patients with a diagnosis of insomnia and no sleep disorder other than insomnia. The COMISA group includes patients with a diagnosis of both OSA and insomnia, diagnosed with both sleep disorders within 1 year and no sleep disorders other than OSA and insomnia. Subjects over the age of 18 years were included.

The SOMNIA study was approved by the medical ethical committee of the Maxima Medical Center (Veldhoven, The Netherlands, N16.074), and all participants provided written informed consent. The protocol for the retrospective data analysis was approved by the Medical Ethical Committee of Sleep Medicine Center Kempenhaeghe and by the Internal Committee of Biomedical Experiments of Philips Research.

The insomnia group appeared to be significantly younger than the OSA and COMISA groups after selecting patients exclusively on diagnosis. Since we are, among other parameters, interested in awakenings during the night and it is known from literature and clinical practice that sleep and wake duration vary with age, we created an age-matched insomnia group.[26] We considered different methods for adjusting for covariates, including analysis of covariance and multiple linear regression. However, our dataset does not meet the assumptions required for these approaches such as equal variance of the dependent variable for each subpopulation. In addition, no statistically significant differences were found for wake variables between sex within the different diagnosis groups. Therefore, matching was the best option to compare the 3 groups, despite the loss of data due to the use of this procedure.[27] First, we classified all patients by age category in bins of 5 years, ie, 21–25, 26–30, 31–35 years, etc. We then assigned a random number to

all patients and sorted the OSA, COMISA, and insomnia groups first on age category and second on random number. Finally, we randomly selected a number of insomnia patients that was proportional to the number of patients for each bin category in the other 2 groups. If the number of insomnia patients for a particular bin category was lower than the number of patients in the OSA or COMISA group, all insomnia patients from that particular bin group were included. This new age-matched insomnia group was used for all statistical analyses, together with the original OSA and COMISA groups.

In OSA, brief awakenings are often related to the termination of breathing events.[23] Apnea-hypopnea index (AHI) was significantly higher for the OSA group compared to the COMISA group. To control for the impact the relationship between a higher AHI and the number and duration of awakenings might have, we performed a subanalysis of variables related to awakenings on an AHI-matched sample for the OSA and COMISA groups. These groups were created using matching, similar to the selection of the age-matched groups. First, we classified all patients in the OSA and COMISA groups by AHI category in bins of 5 breathing events per hour, ie, ≤ 10, $10 < \text{AHI} \leq 15$, $15 < \text{AHI} \leq 20$, etc. We then assigned a random number to all patients and sorted the OSA and COMISA groups first on AHI category and second on random number. Finally, we randomly selected a number of OSA patients that was proportional to the number of patients for each bin category in the COMISA group.

PSG

All participants underwent overnight clinical PSG (Grael PSG, Compumedics, Charlotte, North Carolina). The sleep registrations were performed according to the guidelines of the American Academy of Sleep Medicine[25] and consisted of 6-channel electroencephalogram, 2-channel electro-oculography, and electromyography of the mentalis muscle. In addition, the recordings included electrocardiogram, respiratory flow (nasal and oral thermistors), nasal pressure (nasal cannula), respiratory effort based on thoracoabdominal respiratory inductance plethysmography, oxygen saturation (transmissive finger photoplethysmography), snoring (piezoelectric tracheal microphone), body position (gravity-based electric sensor), and electromyogram of tibialis anterior muscle. Video and sound were recorded throughout the night.

Each PSG recording was evaluated by a single scorer out of a team of 7 certified expert sleep technicians from the Sleep Medicine Center Kempenhaeghe. Sleep and associated events were scored according to the 2015 American Academy of Sleep Medicine criteria, including a > 3% oxygen desaturation from baseline and/or the event associated with an arousal, as recommended for the scoring of hypopneas.[28] In an earlier study, no statistical differences were found between recordings scored by different technicians for sleep onset latency (SOL), WASO, or number of awakenings.[29] Institutional interrater agreement scores according to the American Academy of Sleep Medicine assessment criteria are high, with an average epoch-per-epoch agreement of 85.6% (range 83–88%).

Time in bed was controlled for the PSG measurements. Participants were awakened around 7 AM. Participants had no access to alcoholic or caffeinated drinks in the evening of the PSG after their arrival at the sleep center, the latest at 5 PM.

Study variables

The demographic variables defined for the purpose of this study were age, sex, and body mass index. Sleep-disordered breathing (SDB) parameters included AHI, apnea index, hypopnea index, 3% oxygen desaturation index ($ODI_{3\%}$), and 4% oxygen desaturation index ($ODI_{4\%}$).

PSG-determined awakenings and wake periods were analyzed in detail. At least 1 epoch scored as wake was considered as an awakening. Variables included WASO, number of awakenings during the night, the number of awakenings per hour of sleep, and the mean duration of an awakening. Awakenings were also divided in subgroups according to their length: short awakenings with a duration up to and including 2 minutes, medium-length awakenings with a duration of 2.5 up to and including 4.5 minutes, and long awakenings with a duration of 5 minutes or longer. The threshold of 2 minutes for short awakenings was based on a study by Svetnik et al, who investigated wake bouts in patients with insomnia during treatment.[30] The threshold of 5 minutes for long awakenings was used since this period of continuous wakefulness has been used as a rule of thumb to identify awakenings that could lead to the formation of a memory and suggest increased mental alertness that could progress to an episode of insomnia.[31,32] We also calculated a modified version of WASO containing only awakenings with a duration of 5 minutes and longer ($WASO_{\geq 5\,min}$) to determine the total duration of long awakenings.

In addition, commonly used sleep statistics regarding sleep structure were compared between the groups, including SOL, $SOL_{10\,min}$ (where sleep onset was defined as 10 minutes of consolidated sleep), total sleep time, total recording time, sleep efficiency, sleep-stage percentages (stage N1, stage N2, stage N3, and rapid eye movement stage), and number of sleep-stage transitions.

Finally, we performed an initial exploratory analysis on the AHI-matched sample to investigate the extent to which long awakenings were preceded by a breathing event. For each long awakening, we calculated the time between the end of the closest breathing event and the start of the awakening. Long awakenings were then divided into 3 categories: the breathing event terminates ≤ 30 seconds prior to the start of the awakening, the breathing event terminates between 30 and 60 seconds prior to start of the awakening, or the awakening is not preceded by a breathing event (closest breathing event terminates > 60 seconds prior to the start of the awakening or no breathing event occurs in the period between sleep onset and the start of the awakening).

Statistical analysis

Statistical analyses were carried out in Python (version 3.7).[33] Demographic, SDB, sleep, and wake variables were compared across the 3 disorder groups. First, all variables were tested for normality using the Shapiro-Wilk test. Since only 3 (percentage of N2, N3, and rapid eye movement sleep) out of 24 variables were normally distributed, we decided to report all variables as median with first and third quartiles (Q_1–Q_3) and analyze all data with the nonparametric Kruskal-Wallis H test. Epsilon squared (ε^2) was used to calculate the effect size and was interpreted as follows: 0.00 < 0.01 = negligible; 0.01 < 0.04 = weak;

0.04 < 0.16 = moderate; 0.16 < 0.36 = relatively strong; 0.36 < 0.64 = strong; 0.64 < 1.00 = very strong.[34]

Because multiple variables were compared across groups, a Bonferroni correction was applied. To define an appropriate *P* value we divided the variables in groups of related variables: demographic, SDB, awakening, and sleep statistic variables. The demographic group included 3 variables, namely, sex, age, and body mass index; significance for this group was defined at an alpha value of 0.05/3 = 0.0167. The sleep disturbance variables consisted of AHI, apnea index, hypopnea index, $ODI_{3\%}$, and $ODI_{4\%}$; significance was defined at an alpha value of 0.05/5 = 0.01. The group regarding awakenings included 8 variables: WASO, total number of awakenings, number of awakenings per hour of sleep, mean duration of an awakening, number of short awakenings (duration ≤ 2 minutes), number of medium-length awakenings (duration between 2.5 and 4.5 minutes), number of long awakenings (duration ≥ 5 minutes), and $WASO_{\geq 5\,min}$; significance was defined at an alpha value of 0.05/8 = 0.00625. The sleep structure group contained 10 variables: SOL; $SOL_{10\,min}$; total sleep time; total recording time; sleep efficiency; percentage of time in N1, N2, N3, and rapid eye movement sleep; number of sleep-stage transitions; and number of sleep-stage transitions per hour of sleep. Significance was defined at an alpha value of 0.05/11 = 0.0045. If the Kruskal-Wallis H test was significant, pairwise comparisons were conducted using Mann-Whitney *U* as a post hoc test. We also applied a Bonferroni correction because we tested each pairwise combination of the 3 groups; significance was defined at an alpha value of 0.05/3 = 0.0167.

The Mann-Whitney *U* test was used for the subanalysis regarding awakenings based on the AHI-matched OSA and COMISA group. This analysis included 7 variables: total number of awakenings, number of awakenings per hour of sleep, number of short awakenings, number of medium-length awakenings, number of long awakenings, WASO, and $WASO_{\geq 5\,min}$; significance was defined at an alpha value of 0.05/7 = 0.00714.

RESULTS

Demographic and SDB variables

The initial sample contained 354 participants. There were 199 participants included in the OSA group, 80 in the COMISA group, and 75 in the insomnia group. After randomization, the age-matched insomnia group consisted of 47 patients, while the OSA and COMISA groups were preserved. Therefore, the sample used for analysis contained 326 participants, 109 women and 217 men. Median age was 56.0 years (Q_1: 46.0 to Q_3: 61.0). Demographics, SDB variables, and sleep statistics for each group are listed in **Table 1**. Body mass index was significantly lower for patients with insomnia than for those with COMISA (U = 1,238.0, P < .001) or OSA (U = 3,078.0, P < .001). Some participants in this age-matched group were using hypnotics (OSA: n = 12, COMISA: n = 23, insomnia: n = 14). No data were available on the dose and frequency.

As expected, the insomnia group showed significant lower values on all SDB indices, including AHI, apnea index, hypopnea index, $ODI_{3\%}$, and $ODI_{4\%}$ compared to both the OSA group (U = 1,187.0, 2,184.5, 1,404.0, 1,533.0, and 1,491.5, respectively, and all P < .001) and COMISA group (U = 501.0, 815.5, 562.0, 653.5, and 707.0, respectively, and all P < .001). AHI and $ODI_{4\%}$ were lower for COMISA compared to OSA (U = 6,617.0, P = .014 and U = 6,563.5, P = .011), but no statistically significant differences were found for apnea index, hypopnea index, or $ODI_{3\%}$ between the 2 groups.

There was no statistically significant difference between group medians for SOL, $SOL_{10\,min}$, or total recording time. Total sleep time was significantly longer and sleep efficiency was significantly higher for OSA compared to both the COMISA (U = 5,987.5, P < .001 and U = 5,814.0, P < .001 respectively) and the insomnia group (U = 2,851.0, P < .001 and U = 3,261.0, P < .001, respectively). The percentages of the sleep stages were not significantly different between the 3 groups. The number of sleep-stage transitions during the night for patients with COMISA was significantly lower compared to patients with OSA (U = 6,533.5, P < .01) and significantly higher compared to patients with insomnia (U = 1,166.0, P < .001). However, no statistically significant differences were found for the number of sleep-stage transitions per hour of sleep between the 3 groups.

Awakenings

Detailed statistics of awakenings for each sleep disorder group are shown in **Table 2**. Only the parameters mean duration of awakening and $WASO_{\geq 5\,min}$ showed moderate effect sizes. No statistically significant differences were found among wake variables between the COMISA and the insomnia groups. WASO of patients with OSA was significantly shorter than that of patients with COMISA (U = 6,254.0, P < .01) and of patients with insomnia (U = 3,666.0, P = .01). However, the total number of awakenings during the night and the number of awakenings per hour of sleep were not significantly different between the 3 groups. This resulted in a significantly shorter mean awakening duration for patients with OSA compared to those with COMISA (U = 6,033.5, P < .001) and those with insomnia (U = 3,128.0, P < .001).

The division of awakenings according to different lengths did not reveal a statistically significant difference for the number of short and medium-length awakenings between the 3 groups. However, the number of long awakenings for patients with OSA was significantly lower than for patients with COMISA (U = 6,403.5, P < .01) or with insomnia (U = 3,527.5, P < .01). $WASO_{\geq 5\,min}$ for OSA was also significantly shorter vs COMISA (U = 5,961.5, P < .001) and vs insomnia (U = 3,247.5, P < .001).

Awakenings of the AHI-matched sample

The AHI-matched sample contained 74 participants from the COMISA group and 74 participants from the OSA group. Median AHI for the COMISA group was14.9 events/h (Q_1: 9.9 to Q_3: 25.7) and for the OSA group was 14.5 events/h (Q_1: 10.1 to Q_3: 25.8).

Table 3 shows the subanalysis of awakenings of the AHI-matched sample. The trend in prolonged wakefulness was still visible in the COMISA group compared to the OSA group. The number of long awakenings was higher for COMISA compared to OSA and WASO was longer for COMISA compared to OSA, albeit not statistically significant different after Bonferroni correction. However, $WASO_{\geq 5\,min}$ was statistically significant longer for COMISA compared to OSA.

Table 1—Demographics, sleep-disordered breathing variables, and sleep statistics of the age-matched sample.

	OSA (n = 199)	COMISA (n = 80)	Insomnia (n = 47)	χ^2	*P*	ε^2
Female (% female)	57 (28.6)	32 (40.0)	20 (42.6)	5.3	.070	n.a.
Age, years, median (range) [IQR]	55 (46–62) [22, 81]	55.5 (47.5–60.5) [23, 76]	54 (45.5–61) [21, 76]	0.1	.958	<0.01
BMI, kg/m^2	27.9 (25.3–31.2)‡	27.5 (24.8–29.7)†	24.5 (22.9–27.8)	18.4	<.001	0.057
AHI, events/h	21.6 (12.1–35.4)*‡	16.6 (10.4–28.0)†	6.8 (2.8–11.3)	68.0	<.001	0.209
AI, events/h	1.1 (0.0–3.7)‡	0.5 (0.1–1.9)†	0.0 (0.0–0.2)	36.9	<.001	0.114
HI, events/h	18.1 (10.9–28.6)‡	14.7 (9.8–23.8)†	6.2 (2.6–10.6)	59.4	<.001	0.169
$ODI_{3\%}$, events/h	15.6 (6.6–28.8)‡	10.6 (5.1–22.0)†	2.5 (1.0–5.8)	54.9	<.001	0.169
$ODI_{4\%}$, events/h	8.5 (2.7–16.2)*‡	4.5 (1.7–13.2)†	0.8 (0.2–2.2)	56.4	<.001	0.174
SOL, min	11.0 (5.0–21.8)	12.5 (6.0–29.8)	12.5 (8.3–23.3)	3.5	.176	0.011
$SOL_{10\,min}$, min	21.0 (10.8–39.3)	26.3 (12.9–52.3)	22.0 (15.8–47.5)	3.3	.193	0.010
TST, min	418.5 (374.0–456.5)*‡	391.5 (338.5–436.0)	381.5 (317.5–420.5)	22.8	<.001	0.070
TRT, min	509.0 (489.0–523.3)	504.3 (484.1–523.5)	496.0 (454.3–517.3)	8.3	.016	0.026
SE, %	84.4 (76.4–89.8)*‡	77.3 (70.3–84.6)	78.2 (64.0–85.3)	18.5	<.001	0.057
Time in N1, %	14.6 (10.1–20.1)	12.7 (10.1–19.0)	13.0 (8.3–19.6)	3.5	.175	0.011
Time in N2, %	51.9 (46.7–56.9)	54.2 (46.7–60.5)	52.6 (45.3–59.4)	3.7	.154	0.011
Time in N3, %	16.0 (11.5–20.4)	15.4 (9.5–21.2)	17.3 (11.7–22.9)	1.1	.583	0.003
Time in REM sleep, %	16.0 (12.1–19.7)	16.2 (11.4–19.0)	16.8 (12.2–19.8)	0.5	.769	0.002
Sleep stage transitions, n	218.0 (164.0–272.0)*‡	194.0 (147.5–230.0)†	156.0 (117.0–187.5)	30.3	<.001	0.093
Sleep-stage transition index, n/h	31.5 (23.7–40.7)	30.9 (23.6–39.4)	25.2 (19.6–34.1)	9.0	.011	0.028

Medians with first and third quartile (Q_1–Q_3) values are presented. *OSA is different from COMISA, $P < .0167$. ‡OSA is different from insomnia, $P < .0167$. †COMISA is different from insomnia, $P < .0167$. AHI = apnea-hypopnea index, AI = apnea index, BMI = body mass index, COMISA = comorbid insomnia and sleep apnea, HI = hypopnea index, IQR = interquartile range, n.a. = not applicable, $ODI_{3\%}$ = 3% oxygen desaturation index, $ODI_{4\%}$ = 4% oxygen desaturation index, OSA = obstructive sleep apnea, REM = rapid eye movement, SE = sleep efficiency, SOL = sleep onset latency, $SOL_{10\,min}$ = sleep onset defined as 10 minutes of consolidated sleep, TRT = total recording time, TST = total sleep time.

Long awakenings and breathing events of the AHI-matched sample

The OSA and the COMISA groups had a total of 191 and 248 long awakenings, respectively. In the OSA group, 38 (19.9%) long awakenings were preceded by a breathing event terminating ≤ 30 seconds from the start of the long awakening and 6 (3.1%) between 30 and 60 seconds. In the COMISA group, 34 (13.7%) long awakenings were preceded by a breathing

Table 2—Awakenings of the age-matched sample.

	OSA	COMISA	Insomnia	χ^2	*P*	ε^2
WASO, min	60.0 (36.5–95.5)*‡	83.3 (56.0–112.5)	83.5 (43.3–139.0)	10.7	.005	0.033
Awakenings, n	36.0 (27.0–49.5)	36.0 (26.5–50.0)	32.0 (25.0–42.5)	4.9	.085	0.015
Awakening index, n/h of sleep	5.3 (3.7–7.4)	5.6 (4.3–8.2)	5.4 (3.9–6.7)	1.3	.532	0.004
Mean duration awakening, min	1.4 (1.1–2.2)*‡	2.0 (1.3–2.8)	2.6 (1.4–3.7)	18.7	<.001	0.058
Short awakenings (duration ≤ 2 min), n	28.0 (20.0 – 41.0)	28.0 (20.5–38.5)	23.0 (17.0–35.0)	6.1	.047	0.019
Medium-length awakenings (duration 2.5–4.5 min), n	3.0 (1.0–4.0)	3.0 (1.0–4.5)	2.0 (1.0–3.0)	4.6	.098	0.014
Long awakenings (duration ≥ 5 min), n	2.0 (1.0–3.0)*‡	3.0 (2.0–5.0)	3.0 (2.0–5.0)	11.2	.004	0.034
$WASO_{\geq 5\,min}$, min	25.5 (9.5–51.3)*‡	43.3 (18.8–75.0)	56.0 (19.3–97.5)	17.7	<.001	0.054

Medians with first and third quartile (Q_1–Q_3) values are presented. *OSA is different from COMISA, $P < .0167$. ‡OSA is different from insomnia, $P < .0167$. COMISA = comorbid insomnia and sleep apnea, OSA = obstructive sleep apnea, WASO = wake after sleep onset, $WASO_{\geq 5\,min}$ = wake after sleep onset containing only awakenings with a duration of 5 minutes and longer.

Table 3—Awakenings of the AHI-matched sample.

	OSA	COMISA	*U*	*P*
Awakenings, n	32 (25–45)	36 (26–48)	2,460.5	.14
Awakening index, n/h of sleep	5.0 (3.4–6.8)	5.4 (4.3–8.1)	2,375.0	.08
Short awakenings (duration ≤ 2 min), n	25 (17.0–37.5)	27.5 (20.5–37.0)	2,480.5	.16
Medium-length awakenings (duration 2.5–4.5 min), n	3.0 (1.0–4.0)	3.0 (1.0–4.0)	2,711.0	.46
Long awakenings (duration ≥ 5 min), n	2.0 (1.0–3.0)	3.0 (2.0–5.0)	2,135.5	<.01
WASO, min	57.3 (32.8–94.0)	80.8 (53.8–114.0)	2,109.5	.008
$WASO_{\geq 5\,min}$, min	20.3 (8.8–53.8)	43.0 (18.8–75.0)	2,067.5	.005*

Medians with first and third quartile (Q_1–Q_3) values are presented. *OSA is different from COMISA, $P < .00714$. AHI = apnea-hypopnea index, COMISA = comorbid insomnia and sleep apnea, OSA = obstructive sleep apnea, WASO = wake after sleep onset, $WASO_{\geq 5\,min}$ = wake after sleep onset containing only awakenings with a duration of 5 minutes and longer.

event ending ≤ 30 seconds from the start of the long awakening and 11 (4.4%) within 30 and 60 seconds.

DISCUSSION

The aim of this study was to investigate differences in sleep structure measured with PSG between patients with OSA, COMISA, or insomnia. The main finding was that the duration and frequency of long awakenings is different between the 3 groups. We found that patients with COMISA or insomnia have a longer WASO compared to patients with OSA. Although we expected to find a higher number of awakenings in patients with OSA or COMISA due to brief postobstruction awakenings, the frequency of awakenings did not differ between the groups. This leads to a longer mean duration of an awakening for patients with COMISA or insomnia vs OSA.

By separating awakenings based on their duration, we established that the COMISA and insomnia groups exhibited more long awakenings compared to the OSA group. Although the absolute number of long awakenings does not seem to differ much between the groups, the parameter $WASO_{\geq 5\,min}$ demonstrates the extent of prolonged wakefulness in patients with COMISA or insomnia. This suggests that patients with COMISA are more often awake for a prolonged period, which seems to be distinctive in comparison to patients with OSA. However, only the mean duration of awakenings and $WASO_{\geq 5\,min}$ showed moderate effect sizes, indicating that these parameters alone are not perfectly discriminative between patients with OSA and those with COMISA. Nevertheless, they show a larger effect size compared to the standard wake parameters currently derived from PSG. We speculate that the COMISA group is heterogeneous. Differences on awakenings might be more attenuated for specific phenotypes and less for others, blurring the discriminant power of these PSG markers. A similar trend was found between the COMISA and OSA groups in the AHI-matched sample and highlighted by the statistically significant difference for the variable $WASO_{\geq 5\,min}$. However, in this matched subgroup WASO and the number of long awakenings were not statistically significant different. This could be a consequence of the lower sample size of the OSA group in the AHI-matched sample, influencing statistical power.

No differences were found for short and medium-length awakenings between the 3 groups; short sleep interruptions can lead to nonrestorative sleep and daytime sleepiness, which could explain the overlapping symptoms between OSA and insomnia.[35] In addition, differences in sleep perception between patients with OSA and patients with (comorbid) insomnia could play an important role in the manifestation of symptoms. Patients with OSA may think that they are sleeping through the night and do not perceive sleep fragmentation, while patients with comorbid insomnia are more aware of sleep fragmentation or report experiencing difficulties falling back to sleep even after such a short awakening.[36] This is supported by an earlier suggestion that brief awakenings could contribute to misperception in insomnia.[37]

The absence of the difference in the number of awakenings between the 3 patient groups is in line with 2 other studies.[15,19] However, the separation of awakenings based on various durations and a detailed analysis of the commonly used WASO parameter yielded additional information. This highlights the importance of evaluating awakenings in patients undergoing PSG. Furthermore, the results indicate that caution should be exercised when using home sleep apnea tests to diagnose OSA. It is likely that the diagnosis COMISA will be missed due to the inability to perform sleep staging, and thus the presence of nocturnal wakefulness will be missed.[38]

We found no differences in SOL and $SOL_{10\,min}$ between the 3 groups. We expected to find a greater SOL in insomnia and COMISA patients as this is one of the hallmarks of certain phenotypes of insomnia. A possible explanation for the relatively short SOL in insomnia patients is perhaps related to the specific population examined in this study. The participants were referred to a multidisciplinary expert center for sleep medicine, which may have led to a selection effect: PSG is not performed as part of the routine evaluation of insomnia but is indicated when there is a suspicion of breathing disorders or when initial diagnosis is uncertain, for example due to sleep-state misperception or sleep-maintenance problems.[39] However, the increasing availability of home-based sleep test setups, including electroencephalogram,

indicates the potential to measure sleep objectively in a more accessible way compared to PSG. This offers the chance to measure sleep in more patients suspected of sleep disorders, including insomnia. Another possible explanation for the relatively short SOL in patients with COMISA is the suspicion that COMISA patients mainly experience sleep-maintenance insomnia.[7,40,41] In addition, one should be aware of the phenomenon of covert OSA, where sleep-disordered signs or symptoms such as snoring, sleepiness, and witnessed apneas are absent (or unreported) and reports of insomnia drive the diagnosis and treatment pathway.[42] PSG could reveal a possible effect of an underlying (albeit possibly mild) OSA component that can prevent successful insomnia treatment. Another aspect could be the presence of sleep-state misperception. Sleep-state misperception is a relevant feature within the insomnia population.[37] One of the phenotypes within the COMISA group could be a subgroup with sleep-state misperception. In future work, it would be interesting to collect subjective (perceived) SOL and investigate whether groups differ according to an objective quantification of misperception, for example the Sleep Fragment Perception Index, as described by Hermans et al.[29]

Differences in macrostructural parameters could help in identifying patients with COMISA at an early stage. This highlights one of the main strengths of this study, since the metrics derived in this study are calculated based on the standard available PSG metrics, with the advantage that no additional labor-intensive scoring is needed. However, the high costs, time-consuming evaluation, and obtrusive nature of PSG often limit it to the measurement of a patient's sleep for a single night, and the first-night effect could influence the sleep measurement, as it is known that in both ambulatory and laboratory settings PSG can alter sleep quality and increase sleep fragmentation.[43] Patients with insomnia may actually sleep better in such a setting, although this does not seem to be the case in this study.[44] Furthermore, night-to-night variability could play a role in the assessment of insomnia and is therefore likely to play a role in COMISA as well. Newly developed technologies can play a pivotal role in overcoming these limitations. Surrogate measurements of sleep show improvements in the detection of wake, providing an opportunity for the measurement of objective sleep and duration of awakenings in a nonobtrusive manner. The proposed wake parameters could be easily calculated from these measurements. The analysis of several consecutive nights, preferably with a nonobtrusive method that can accurately measure sleep at home, could reveal additional insights regarding the manifestation and pathophysiology of the comorbid condition. In addition, the assessment of subjective measurements, for example questionnaires, could provide information that is useful to distinguish patients with OSA, COMISA, or insomnia.

Research into the cause of awakenings could help develop a better understanding of COMISA and its diagnosis. For example, it would be interesting to investigate the relationship between SDB events and to what extent these trigger, initiate, or even follow short and long awakenings. Surprisingly, we found no difference in the number of short awakenings between the 3 groups. We expected that a higher AHI would lead to more sleep fragmentation and thus more short awakenings. However, these short awakenings are also present in patients with insomnia. This begs the question of what causes these frequent, brief awakenings in insomnia. Is the cause of awakenings in patients COMISA the same as the cause of awakenings in patients with pure OSA or patients with pure insomnia? A first exploratory analysis did not reveal a clear time relation between breathing events and long awakenings between patients with OSA and those with COMISA. However, to the best of our knowledge there are no formal rules to link breathing events with awakenings. Therefore, we recommend performing an extensive analysis on the (time) relationship between breathing events and awakenings in a future study. A hypothesis could be that smaller respiratory disturbances or shallower, shorter desaturations lead to earlier termination of respiratory events, for example by arousal or awakening in COMISA patients, compared to the larger disturbance needed to awake OSA patients; this could be indicative of a lower arousal threshold in the COMISA group. In addition, psychophysiological mechanisms involved in chronic insomnia, such as rumination and mental alertness, could turn a series of arousals or brief postobstruction awakenings into an episode of insomnia. This type of research could reveal distinct phenotypes of COMISA requiring different treatment strategies. We can speculate that one phenotype may be characterized by long awakenings caused by breathing events. In this case, insomnia would be a symptom of OSA, where treatment with continuous positive airway pressure could be successful in alleviating the symptoms of both conditions.[40] In another phenotype, we hypothesize that there might not be a relationship between episodes of insomnia and breathing events, in which case OSA and insomnia simply coexist. These patients could benefit from initial cognitive behavioral therapy for insomnia followed by continuous positive airway pressure therapy or parallel treatment with both therapies.[45] In the current study, we focused on awakenings of varying duration. Manual scoring of arousals is currently not available for our dataset, but in the future it could be interesting to also investigate the role of arousals in this context.

A possible limitation of this study is that data were collected at a multidisciplinary expert center for sleep medicine. This, together with the fact that PSG is not routinely performed in patients with insomnia in the absence of other sleep concerns and the lack of information concerning potential symptoms for additional sleep disorders, could have biased our insomnia sample. Therefore, we recommend investigating the proposed wake parameters in prospective clinical cohorts, for example in patients who were diagnosed at first- or second-line clinics.

Another limitation of this study pertains to the use of hypnotics by several participants. In our clinic, patients who report frequently using hypnotics are allowed to take their medication during the PSG night, while it is discouraged for patients who use hypnotics infrequently. However, we do not have information about which patients indeed used hypnotics during PSG. Nevertheless, we do not expect that this had a negative impact on the results. We focus on awakenings and therefore expect that the use of hypnotics, at the very least, would not increase WASO or $WASO_{\geq 5\,min}$.[46] Since the percentage of COMISA participants using hypnotics was higher than in the OSA group, it is in fact possible that the differences in WASO and $WASO_{\geq 5\,min}$ between patients with OSA and COMISA are even more pronounced

when patients would not have been allowed to use hypnotics during PSG. We recommend investigating the influence of hypnotic use on WASO and $WASO_{\geq 5\,min}$ in future studies in a controlled setting.

To our knowledge, this is the first detailed analysis of awakenings in patients with pure OSA, pure insomnia, and COMISA. Differences in the length and number of long awakenings were found between patients with OSA, COMISA, or insomnia, which may provide diagnostic value. Patients with COMISA have brief awakenings that can also be found in the PSG sleep measurement of both OSA and insomnia patients, but COMISA patients also experience wakefulness for prolonged periods during the night, which is one of the hallmarks of insomnia. In addition, the presence of SDB may also contribute to sleep fragmentation in patients with COMISA. This suggests that patients with COMISA experience the additive adverse components of sleep disturbance from both OSA and insomnia, potentially resulting in decreased sleep quality and worse clinical outcomes compared to having either one or both conditions.

ABBREVIATIONS

AHI, apnea-hypopnea index
COMISA, comorbid insomnia and sleep apnea
ICSD, *International Classification of Sleep Disorders*
$ODI_{3\%}$, 3% oxygen desaturation index
$ODI_{4\%}$, 4% oxygen desaturation index
OSA, obstructive sleep apnea
PSG, polysomnography
SDB, sleep-disordered breathing
SOL, sleep onset latency
$SOL_{10\,min}$, sleep onset latency where sleep onset is defined as 10 minutes of consolidated sleep
SOMNIA, Sleep and OSA Monitoring with Non-Invasive Applications
WASO, wake after sleep onset
$WASO_{\geq 5\,min}$, wake after sleep onset containing only awakenings with a duration of 5 minutes and longer

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