ORIGINAL ARTICLE

Sleep-related cortical arousals in adult subjects with negative polysomnography

Nattapong Jaimchariyatam · Carlos L. Rodriguez · Kumar Budur

Abstract

Purpose The arousal index (AI) quantifies cortical arousal relative to total sleep time and is widely used to determine the severity of sleep fragmentation. It usually includes arousals secondary to respiratory events, limb movements, and spontaneous arousals. No systematic studies have been undertaken to determine AI cutoff in subjects with negative polysomnography.

Methods Three hundred fifty polysomnograms of subjects ≥18 years of age with no sleep disorders (apnea-hypopnea index (AHI) <5, periodic limb movement index (PLMI) <10, no upper airway resistance syndrome) or minimum oxygen saturation >90 % and no comorbid health problems were reviewed.

Results Basic sleep architecture appears within normal range, except for increased stage N2 and decreased stage N3. AI significantly correlated with age ($r=0.7$), sleep efficiency ($r=-0.16$), sleep latency ($r=0.14$), rapid eye movement (REM) latency ($r=0.12$), stage N1 ($r=0.15$), stage N2 ($r=0.12$), stage N3 ($r=-0.27$), AHI ($r=0.24$), PLMI ($r=0.18$), and nadir oxygen saturation ($r=-0.17$) [$p<0.05$ for all]. A significant correlation was noted between age and sleep efficiency ($r=-0.19$), REM latency ($r=0.13$), stage N1 ($r=0.16$), stage N2 ($r=0.21$), stage N3 ($r=-0.39$), and nadir oxygen saturation ($r=-0.16$) [$p<0.05$ for all]. Multiple linear regression analysis showed that age is only the independent predictor of AI ($R^2=0.70$, $p<0.01$). The prediction equation for the arousal index in subject with negative polysomnography is AI=0.276×age (year)+8.018.

Conclusions Age is the most important independent factor in predicting increasing AI in subjects with negative polysomnography.

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Abbreviations

OSAS	Obstructive sleep apnea syndrome
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
TST	Total sleep time
PSG	Polysomnogram
AHI	Apnea-hypopnea index
RDI	Respiratory disturbance index
AI	Arousal index
PLMI	Periodic limbs movements index
PLMAI	Periodic limbs movements arousal index
BMI	Body mass index
CPAP	Continuous positive airway pressure
REM	Rapid eye movement
SPSS	Statistical Package for the Social Sciences
EOG	Electrooculogram
EMG	Electromyogram
ECG	Electrocardiography
SpO2	Pulse oxygen saturation

WASO   Wake after sleep onset
ASDA   American Sleep Disorders Association

Introduction

Arousals are known to reflect a progressive activation from the subcortical to the cortical region [1, 2] and subcortical arousals often consist of autonomic and brainstem arousals, which can occur without any changes in cortical activity [3, 4]. Sleep fragmentation characterized by repetitive short sleep interruptions is one of the recognized determinants of excessive daytime sleepiness [5]. Notwithstanding, the measurement of cortical arousals during sleep is useful in quantifying sleep fragmentation, though numerous variables have been examined to characterize this complex physiology of sleep. Cortical arousal refers to brief abrupt increases in electroencephalographic (EEG) frequency, mostly alpha and beta (excluding spindle), that interrupt the continuity of the sleep state background with or without accompanied increases in chin electromyographic (EMG) activities. The arousal index (AI) quantifies cortical arousal relative to total sleep time and is widely used to determine the severity of sleep fragmentation. The arousal index usually includes arousals secondary to respiratory events, limb movements, and spontaneous arousals. Each of these arousals can be classified by changes in EEG frequency, EMG amplitude, and/or the presence of limb movements. New measurements to quantify sleep fragmentation have been developed, including other measures of EEG activity (e.g., cyclic alternating pattern (CAP)) [6–8] and measures of autonomic activity (e.g., pulse transit time (PTT) or peripheral arterial tonometry (PAT)) [9–12]. However, the American Academy of Sleep Medicine (formerly, the American Sleep Disorders Association (ASDA)) 3-s rule is still the most widely used definition of arousal in the majority of sleep laboratory [13, 14] and scoring EEG arousal is thus far the best validated approach for quantifying sleep fragmentation, with relatively high reliability and validity [7, 14]. In addition, the significance of autonomic arousals that are not associated with EEG arousals in contributing to daytime impairment is uncertain and studies have not shown that autonomic arousals without EEG arousals are predictive of daytime sleepiness [10, 13, 15]. Studies in human have reported, in correlation with increasing cortical arousals, increased objective and subjective sleepiness [5, 16–18], decreased psychomotor performance [16–18], changes in hormone secretion patterns [19], decreased upper airway function [20], increased whole body metabolic rate [21], and increased sensory arousal thresholds [22, 23], as compared to baseline. It is therefore very important to quantify cortical arousals accurately and identify the norms of arousal index in polysomnogram (PSG).

Age-dependent alterations in sleep architecture include a decrease in total sleep time, reduced sleep efficiency, and decreased percentage of slow wave sleep and rapid eye movement (REM) sleep [24, 25]. Regarding a correlation between aging and arousals, there has been minimal evidence indicating that the number of brief arousals, like other metrics of sleep quantity, was influenced by increasing age [25–28]. In those studies, however, sleep was recorded from normal and sleep-related breathing disorders subjects [25, 27, 28] or respiratory events were measured by limited procedure (i.e., no nasal pressure transducer or abdominal effort detector) [26].

We therefore hypothesized that sleep-related cortical arousals in apparently normal subjects, as indicated by negative polysomnography and absent coexisting sleep disorders, will increase with increasing age. The second purpose was to identify the other factors influencing sleep-related cortical arousals and to identify the norms of sleep-related cortical arousals in those subjects. Accordingly, this study was undertaken to evaluate the correlation between sleep-related cortical arousals and age and to identify the norms of age-dependent sleep-related cortical arousals.

Methods

The clinical interview, sleep questionnaire, and polysomnographic raw data of 12,719 patients who attended at Cleveland Clinic Sleep Disorders Center, Ohio, from July 2005 to October 2008 were reviewed. Given that the studies performed before 2007 were scored according to previous PSG criteria, all chosen polysomnograms of candidates satisfying the inclusion and exclusion criteria were then rescored to see if they satisfied the American Academy of Sleep Medicine (AASM) scoring criteria 2007. All polysomnograms were performed using a standard procedure, including video recording, left and right electrooculogram (EOG), central and occipital electroencephalogram (EEG), mental and submental electromyogram (EMG), left and right anterior tibialis EMG, single electrocardiogram (ECG) waveform, snoring, continuous airflow with thermistor, nasal pressure transducer, chest and abdominal effort, and oxygen saturation with pulse plethysmography. Sleep stages were scored according to standard AASM 2007 criteria [29] on 30-s epoch, as follows: wakefulness and sleep stage non-rapid eye movement (NREM) 1, 2, and 3&4 (stages N1, N2, and N3, respectively) and REM sleep. Cortical arousal in this study was scored using the criteria proposed by ASDA [13]. Arousal was identified as an abrupt shift in EEG frequency, which may include theta, alpha, and/or frequencies greater than 16 Hz, but not spindle. Ten seconds of continuous sleep must have preceded the arousal and the arousal must last ≥3 s and must have been accompanied by an increase in chin EMG if it occurred during REM sleep.

We limited this study to subjects who met the following criteria:

(1) Age ≥18 years;
(2) Apnea-hypopnea index (AHI) <5/h (apnea was defined as airflow cessation for more than 10 s and hypopnea was defined as nasal pressure signal excursions (or those of the alternative hypopnea sensor) that drop by ≥50 % of baseline and the duration of this drop lasted at least 10 s and was associated with a decrease in oxygen saturation of at least 3 % or followed by an arousal);
(3) Periodic limb movement index <10/h;
(4) Adequate polysomnogram as determined by total sleep time more than 6.5 h and a sleep efficiency of ≥65 %;
(5) Minimum oxygen saturation >90 % (The oximetry data was visually reviewed to identify its association with an acceptable plethysmographic signal. All SpO_2 values were calculated only sleep to decrease the impact of wake after sleep onset (WASO) on oxygen saturation);
(6) Absence of cardiopulmonary, neurological, and psychiatric disorders;
(7) Absence of previously diagnosed sleep disorders identified by clinical interview or sleep questionnaire; and
(8) Absence of findings suggestive of upper airway resistance syndrome (UARS) as determined by respiratory disturbance index (RDI) greater than 5/h. (RDI is similar to the AHI. However, RDI also includes respiratory events that do not technically meet the definitions of apneas or hypopneas but do disrupt sleep. This is also referred to as respiratory effort related arousal (RERA). For this study, RERA was defined as either snoring-related arousal, crescendo-related arousal, or inspiratory flow limitation-related arousal).

Clinical interviews were reviewed and subjects were excluded if they described current use of sedatives, hypnotic, or other medications known to cause sleep disturbance; the use of alcohol (>7 drinks/week); or illicit drug abuse. Positive airway pressure (PAP) titration studies, including split and full night studies, were also excluded. Candidates with other co-morbidities that resulted in sleep disturbance or sleep fragmentation, such as cardiopulmonary, neurological, pain syndrome, and other medical and psychiatric disorders, were also excluded. Subjects diagnosed with any sleep disorders after the initial PSG, at any time before the study enrollment, were also excluded from the study. The clinical or office interviews and sleep questionnaires, including available investigations, were reviewed for these purposes.

According to these inclusion and exclusion criteria, 361 subjects were selected from our database and their PSGs were rescored using AASM 2007 scoring criteria. All scoring was performed by one of our three readers (authors) and then systematically reviewed. After rescoring, 350 subjects were included into statistical analysis. This study was approved by the Institutional Review Board (IRB) at the Cleveland Clinic, Cleveland, Ohio, USA.

Data on the following variables were collected: age, gender, body mass index (BMI), past medical history, Epworth Sleepiness Scale (ESS) scores, sleep efficiency, sleep and REM latencies, sleep stage distribution, arousal index, AHI, RDI, periodic limb movement index (PLMI), periodic limb movement arousal index (PLMAI), and nadir oxygen saturation.

Data analysis

Data analysis was performed using SPSS version 11.5 and JMP version 6.1. Sample size was estimated at 336, based on previous data, a power of 0.9, and alpha of 0.05 [25–28]. Database characteristics with normal distribution were summarized and expressed as mean but otherwise as median or ratio (%). To determine whether the distributions of all continuous data were normal, a Kolmogorov-Smironov test was

Table 1 Demographic and polysomnographic data of all subjects (n=350)

Covariates[a]	Data[b]
Age (years)	54.21±19.78
Male/female (%/%)	51.71:48.29[c]
Neck circumference (cm)	37.53±4.48
BMI (kg/m²)	29.97±8.26
ESS	6.96±3.90
Sleep efficiency (%)	80.10±9.00
Sleep latency (min)	20.80±19.55
REM latency (min)	113.68±59.20
Stage 1 (% of TST)	9.53±6.20
Stage 2 (% of TST)	62.46±8.80
Stage 3&4 (% of TST)	7.42±7.18
REM (% of TST)	20.65±5.18
AHI	1.68±1.51
RDI	2.01±1.17
Arousal index	13.32±8.42
PLMI	2.28±3.56
PLMAI	0.61±1.12
Nadir oxygen saturation (%)	92.25±2.40

BMI body mass index, *ESS* Epworth Sleepiness Scale, *REM* rapid eye movement, *TST* total sleep time, *AHI* apnea-hypopnea index, *RDI* respiratory disturbance index, *PLMI* periodic limbs movements index, *PLMAI* periodic limbs movements arousal index

[a] Distributions of all continuous data are normal except for those relating to gender

[b] All data are presented as mean±SD except for gender, which is expressed as percentage (%)

[c] There was no statistically significant difference between the number of men and women (p>0.005)

Table 2 Correlation between arousal index and various covariates (n=350)

Covariates[a]	Correlation coefficient (r)[b]	p value
Age	0.696	p<0.001
Neck circumference, cm	0.094	p=0.078
BMI, kg/m^2	0.006	p=0.905
ESS	0.106	p=0.047
Sleep efficiency, %	−0.160[c]	p=0.003
Sleep latencies, minutes	0.136	p=0.011
REM latencies, minutes	0.121	p=0.024
Stage 1 sleep, % of TST	0.150	p=0.005
Stage 2 sleep, % of TST	0.120	p=0.025
Stage 3&4 sleep, % of TST	−0.268	p<0.001
REM sleep, % of TST	−0.140	p=0.794
AHI, events/h	0.235	p<0.001
RDI, events/h	0.332	p<0.001
PLMI, events/h	0.176	p<0.001
PLMAI, events/h	0.249	p<0.001
Nadir oxygen saturation, %	−0.165	p=0.002

BMI body mass index, *ESS*, Epworth Sleepiness Scale, *REM* rapid eye movement, *TST* total sleep time, *AHI* apnea-hypopnea index, *RDI* respiratory disturbance index, *PLMI* periodic limbs movements index, *PLMAI* periodic limbs movements arousal index

[a] Distributions of all continuous data are normal

[b] Pearson correlation coefficient for parametric data and Spearman's rho for nonparametric data

[c] Minus sign (−) represents inverse correlation

Table 3 Correlation between age and various covariates (n=350)

Covariates[a]	Correlation coefficient (r)[b]	p value
Neck circumference, cm	0.068	p=0.205
BMI, kg/m^2	−0.016	p=0.770
ESS	0.101	p=0.050
Sleep efficiency, %	−0.188	p<0.001
Sleep latencies, minutes	0.071	p=0.187
REM latencies, minutes	0.129	p=0.016
Stage 1 sleep, % of TST	0.160	p=0.003
Stage 2 sleep, % of TST	0.208	p<0.001
Stage 3&4 sleep, % of TST	−0.388	p <0.001
REM sleep, % of TST	−0.008	p=0.886
AHI, events/h	0.125	p=0.019
RDI, events/h	0.143	p=0.011
Arousal index	0.696	p<0.001
PLMI, events/h	0.079	p=0.142
PLMAI, events/h	0.120	p=0.025
Nadir oxygen saturation, %	−0.159	p=0.003

BMI body mass index, *ESS* Epworth Sleepiness Scale, *REM* rapid eye movement, *TST* total sleep time, *AHI* apnea-hypopnea index, *RDI* respiratory disturbance index, *PLMI* periodic limbs movements index, *PLMAI* periodic limbs movements arousal index

[a] Distributions of all continuous data are normal

[b] Pearson correlation coefficient for parametric data and Spearman's rho for nonparametric data

[c] Minus sign (−) represents inverse correlation

performed. Pearson correlation was used to analyze the correlation between arousal index and various continuous variables and between aging and various continuous variables. Otherwise, one-way ANOVA with post hoc or contrast test was used. Across different age groups, overall differences between macro-structural parameters, number of arousals, and arousal indices were analyzed by one-way ANOVA. Multiple linear regression analyses were performed to evaluate the contribution of each basic demographic and sleep variable to models predicting the arousal index. Collinearity among the variables in the regression model was measured by means of tolerance and the variance inflation factor (VIF). Statistical significance was set at p<0.05.

Results

A total of 364 subjects matched the inclusion and exclusion criteria for this study and were then rescored using AASM 2007 criteria. Fourteen rescored subjects were excluded because they no longer met the inclusion and exclusion criteria. Thus, a total of 350 subjects remained for final analysis. Demographic data and polysomnographic variables are shown in

Table 1. The indication for performing PSG included snoring (340/350, 97.14 %), witnessed apneas (211/350, 60.29 %), excessive daytime sleepiness (289/350, 82.57 %), daytime fatigue (339/350, 96.86 %), and recurrent awakenings from sleep or maintenance insomnia (299/350, 85.43 %). The majority had more than one indication (342/350, 97.71 %).

As noted in Table 1, these individuals had no apparent obstructive sleep apnea and no increased periodic limb movement. The overall sleep architecture appeared relatively normal with only slightly decreased slow wave sleep and slightly prolonged sleep and REM sleep onset latency. There was no significant difference between the number of men and women (p>0.005). These individuals also had relatively high average BMI in the upper normal limits (29.97±8.26). Subjects spent 81.2 % of sleep time in the supine position. In the morning questionnaires, all subjects reported the quality and quantity of the previous night's sleep as satisfactory and similar to their habitual sleep at home.

The arousal index was significantly predicted by age (p<0.001), ESS (p<0.05), sleep efficiency (p<0.05), sleep and REM sleep onset latencies (p<0.05), NREM sleep (p<0.05), AHI (p<0.001), RDI (p<0.001), PLMI and PLMAI (p<0.001), and finally nadir oxygen saturation (p<0.01) [Table 2]. There was no statistically significant difference between the arousal

Table 4 Determinants of arousal index as evaluation by multiple linear regression analysis (n=350) (Dependent variable: arousal index)

Parameter[a,b,c]	Unstandardized coefficients (b)	Standard error of (b) [SE_b]	Standardized coefficients (B)	t	p value[d]
Age	0.276	0.018	0.648	15.381	$p<0.001$
Sleep efficiency (% of TST)	−0.018[e]	0.038	−0.019	−0.467	$p=0.641$
Sleep latency (min)	0.034	0.017	0.079	2.00	$p=0.056$
REM latency (min)	0.003	0.006	0.023	0.576	$p=0.565$
Sleep stage 1 (% of TST)	0.015	0.075	0.011	0.195	$p=0.845$
Sleep stage 2 (% of TST)	−0.022	0.063	−0.023	−0.354	$p=0.723$
Sleep stage 3&4 (% of TST)	−0.012	0.077	−0.010	−0.157	$p=0.875$
AHI (/h)	0.029	0.019	0.069	1.59	$p=0.066$
RDI (/h)	0.039	0.022	0.112	3.66	$p=0.055$
PLMAI (/h)	0.024	0.012	0.055	1.10	$p=0.063$
Nadir oxygen saturation (%)	−0.105	0.139	−0.030	−0.751	$p=0.453$

Constant unstandardized coefficient=8.018; SE_est (standard error of the estimate)=±5.8332; correlation coefficient (R)=0.731; R^2=0.534; F value=38.880; $p<0.001$

BMI body mass index, *ESS* Epworth Sleepiness Scale, *TST* total sleep time, *AHI* apnea-hypopnea index, *t* t test in multiple linear regression model

[a] The independent variables all enter in the statistical analysis in the single step using "All Enter" method

[b] Distributions of all continuous data are normal

[c] Impact of collinearity among the variables in this linear regression model was measured by means of tolerance and the variance inflation factor (VIF) and there was no multicollinearity found in this regression model

[d] p values are expressed as tests of linear trend

[e] Minus sign (−) represents inverse correlation

index of men compared with that of women ($p=0.213$). In addition and as shown in Table 3, we found a significant association between age and sleep efficiency ($p<0.001$), REM latency ($p<0.05$), NREM sleep ($p<0.05$), AHI ($p<0.05$), RDI ($p<0.05$), arousal index ($p<0.001$), PLMAI ($p<0.05$), and nadir oxygen saturation ($p<0.01$). The correlation between age and ESS was nearly statistically significant ($p=0.05$). Nevertheless, increasing age was found to be the most important predictor of arousal index after controlling of contributing factors by means of the multiple linear regression analysis (Table 4 and Fig. 1). Further, the equation predicting increasing arousal index can be calculated by using the regression formula as follow: arousal index (/h)=0.276×age (year)+8.018.

Considering individuals in different age groups, post hoc tests revealed that the arousal index was significantly lower in those 59 years or younger, as compared with older individuals (Table 5 and Fig. 2). No gender-related differences in terms of arousal index were detected across all age groups ($p>0.05$).

Fig. 1 Correlation between arousal index and aging in "negative polysomnography individuals." The figure showed that arousal index significantly linearly correlates with increasing age [n=350; R^2=0.4534, $p<0.001$] as described by scatter plot with regression lines. The equation predicting arousal index (Y-axis) using age (X-axis) is as shown: $Y=0.276X+8.018$
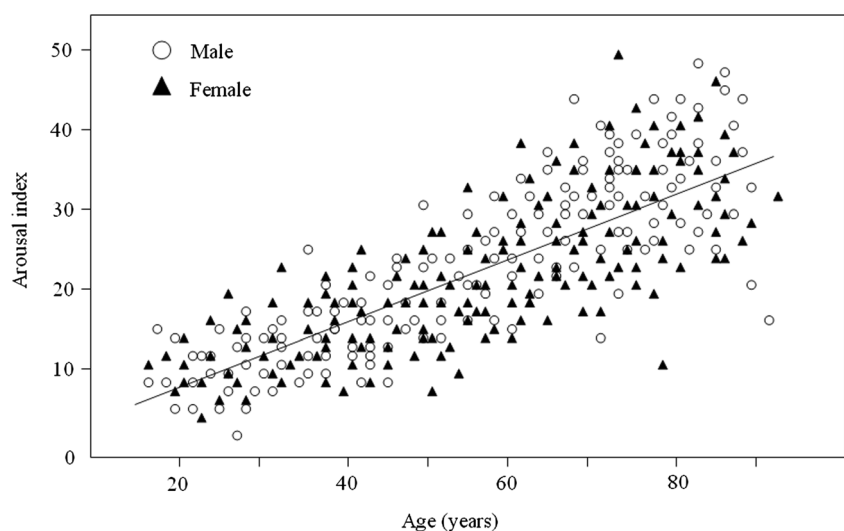
Table 5   Distribution of arousal index in different age groups

| Age group	Number	Mean	Standard deviation	Standard error	95 % confidence interval
18–29	43	6.84	3.32	0.51	5.82–7.86
30–39	57	6.63	3.80	0.50	5.62–7.64
40–49	50	8.72	4.51	0.64	7.44–10.00
50–59	50	11.03	5.70	0.81	9.41–12.65
60–69	50	17.60	8.08	1.14	15.31–19.90
70–79	54	20.57	7.08	0.96	18.63–22.50
≥ 80	46	21.98	6.95	1.02	12.43–14.20
Total	350	13.32	8.42	0.45	12.70–19.40

Discussion

In this study, we used the database of standardized PSG, sleep questionnaire, and clinical interview. Only one night PSG was included for analysis. This results in some limitations resulting from the first night effect and different PSG criteria used for scoring the study before and after 2007. To reduce these limitations, we rescored the study again using AASM 2007 scoring criteria and, fortunately, the data revealed only minor first night effect on PSG results (very slightly delayed sleep and REM onsets, as well as slightly decreased slow wave sleep). Night-to-night variability in terms of macro and microstructure of sleep might be the case, even though the effect on the arousal index should be small. Sleep deprivation prior to the day of PSG (which can influence the arousal index) was also not controlled.

On the morning questionnaires, all subjects reported their night's sleep as satisfactory and similar to their habitual sleep at home. Subjects sound somewhat nearly obese (BMI, 29.97 ±8.26); none, however, were ever diagnosed with any sleep disorders. Pediatrics subjects (age <18 years) were not included in this study; thus, our findings could not be generalized to those age groups. We also followed up all included subjects to make sure that none were diagnosed with any sleep disorders prior to the completion of this research manuscript. The findings in this study should thus be generalizable to "healthy" adults. In this study, we did not measure respiratory effort in order to diagnose UARS, which may limit the validity of UARS diagnosis. In addition, arousals related to sleep position changes were not analyzed. These issues may limit the validity of the study conclusion. Additionally, the visual scoring of cortical arousal as used in this study corresponded to complete arousals, which included both cortical and autonomic activation. Thus, the arousal reactions that included autonomic, but no cortical changes (the so-called subcortical arousal), that could not be visually scored in this study might have led to a different outcome. However, scoring EEG arousal based on AASM 2007 scoring criteria is, to date, the best validated approach, with relatively high reliability and validity in quantifying sleep fragmentation [7, 14].

The change in sleep architecture with aging, including sleep efficiency, REM sleep onset latency, NREM sleep distribution, respiratory and leg movement events, and nadir oxygen saturation is somewhat similar to the previous studies [24–28]. The most prominent changes include reduction in sleep stage 3&4 and increased arousal index. Gender has been found to account for differences in sleep measures [25], but this study did not undertake to verify this difference; thus, the effect of gender on sleep architecture could not be determined. However, in subgroup analysis, the effect of gender on arousal index in different age groups was statistically insignificant.

Based on our review of the literature, this is the first large study to explore the effect of aging on increasing arousal index in negative polysomnography individuals who have never been diagnosed with any sleep disorders using standard full channel PSG. The effect of aging on increasing arousal index

Fig. 2 Distribution of arousal index in different age groups
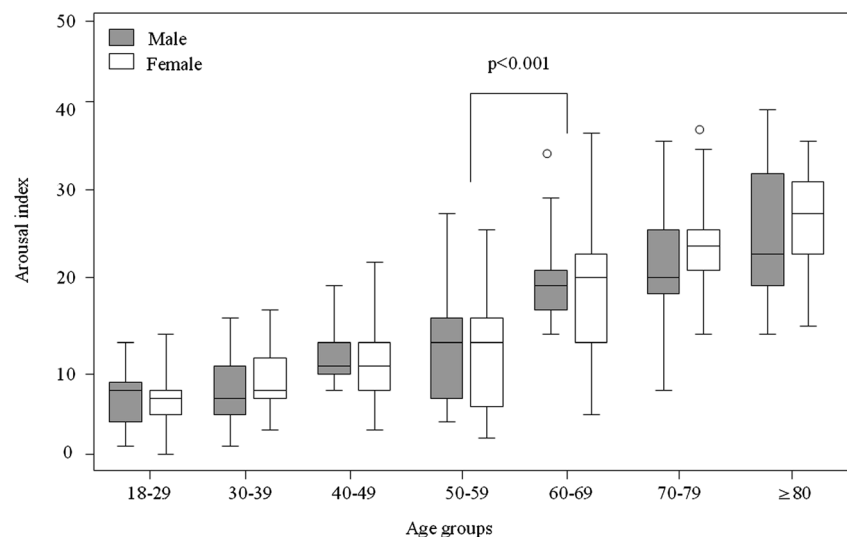
has been widely described. Redline et al. [25] published data from the Sleep Heart Health Study (SHHS) and revealed that the mean (±SD) significantly, although relatively small, increase with age, ranging from 16 (±8.2) for the age 37–54 years old group to 18.4 (±10) for the 55–61 years old group, to 20.3 (±10.5) for the 62–70 years old group, and to 21 (±11.6) for those older than 70 years. However, the study included subjects with sleep-related breathing disorders and revealed that RDI was by far the single most powerful predictor of increasing cortical arousals. Boselli et al. [26] reported the distribution of EEG arousals quantified under limited PSG recording (no air flow or respiratory effort detection) in normal sleepers (no ESS data) of different age groups (10–19, 20–39, 40–59, and ≥60 years) and they found an evolution with age of arousal frequency during total sleep time ($r=0.852$, $p<0.001$). Mathur et al. [27] reported a positive correlation between age and cortical EEG arousals. However, sleep studies were recorded form a total of 55 subjects, including both normal subjects and subjects with sleep-related breathing disorders. Given that total sleep time (TST) varies across age groups, Boselli et al. [26] found that the increase of arousal index/TST was mainly charged to NREM sleep, especially in sleep stages 1 and 2, rather than to REM sleep. Recently, a large cohort study from Brazil revealed that, in the general population (both men and women), a large effect size was observed for the age-related increase in arousal index and WASO; however, the increase in the arousal index was mainly due to respiratory-related arousals [28].

Unlike previous studies in which limited PSGs were mostly used, few subjects were involved, and SBD patients were included, our study included adequate number of subjects and none of these had any sleep, medical, or psychiatric disorders that could have potentially influenced the arousal index and sleep architecture. Although all of the subjects were symptomatic at the time the polysomnogram was being performed, none of them had been diagnosed with any sleep disorders at the time of enrollment. In unadjusted analyses, the arousal index was influenced by age, ESS, sleep efficiency, sleep and REM sleep onset latency, NREM sleep, AHI, RDI, PLMI and PLMAI, as well as nadir oxygen saturation. However, after adjusting and controlling for ESS, sleep efficiency, sleep and REM sleep onset latency, NREM sleep, AHI, RDI, PLMI and PLMAI, as well as nadir oxygen saturation, we found age to be the most significant influence on arousal index in negative polysomnography individuals. We were also able to formulate an equation that can calculate the norms for arousal index for different age groups in "negative polysomnography" adults (age >18 years), as follows: Arousal index (/h) $= 0.276 \times$ age (year) $+ 8.018$.

In conclusion, this study demonstrated the significant effect of age on sleep architecture and arousal index, as identified in the literatures. However, this study included a large number of subjects and none of these had any sleep, medical, or psychiatric disorders. Normal aging increases the number of EEG arousals throughout sleep, after controlling for the other contributing factors. An equation predicting the norms for cortical EEG arousals for "negative polysomnography" or "apparently healthy" adults (age >18 years) is also disclosed for consideration and review. However, determining a cutoff may not be the ideal way to measure norms for arousal indices. Measuring norms by ranging or including autonomic arousals should be determined significant.

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