ORIGINAL ARTICLE

Sleep profile in a population of community-dwelling nonagenarians: data from the Mugello study

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Abstract

Background: Very few studies have investigated sleep characteristics in the oldest-old individuals (aged ≥85 years) and data collected often rely on self-reported information. This study had three aims: (i) to objectively assess, using a wearable device, the sleep characteristics of a large community of oldest-old subjects; (ii) to assess differences in sleep parameters between self-reported 'good sleepers' and 'bad sleepers'; (iii) to assess whether there was a relationship between sleep parameters and cognitive status in this community-dwelling population.

Methods: There were 178 subjects (74.2% women, median age 92 years) included in the 'Mugello study', who wore an armband 24 h/day for at least two consecutive nights to estimate sleep parameters. The perceived sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), the cognitive status through the Mini-Mental State Examination. Continuous variables were compared between men/women, and good/bad sleepers with the independent *t*-test or Mann–Whitney *U*-test, according to data distribution. Chi-square test was used for categorical/dichotomous variables. An ordinal logistic regression model was used to study the possible association between sleep parameters and cognitive function.

Results: Participants spent in bed nearly 9 h, with a total sleep time of 7 h, a sleep onset latency of 17 min, and a sleep efficiency of 83%. Sleep onset latency was significantly associated with different cognitive levels when age and education level were considered. No significant difference in sleep parameters estimated using the SenseWear armband were found between poor (n = 136, 76.4%) and good sleepers (n = 42, 23.6%), identified according to the PSQI.

Conclusions: In this study, actigraphic measurements revealed that subjects with a cognitive decline were more prone to increased sleep onset latency. Sleep quality assessed using the PSQI was not coherent with actigraphic measurements in this sample, supporting the need for objective measures when investigating sleep quality in the oldest-old population.

Key words: actigraphy, Mini-Mental State Examination, nonagenarians, sleep, sleep quality.

INTRODUCTION

The structure of sleep (sleep duration, sleep stages, quantity, and quality of sleep oscillations) modifies with age.¹ Advancing into the fifth decade of older age and beyond, there are several well-characterised changes in sleep architecture: advanced sleep

timing, longer sleep onset latency, shorter overall sleep duration, increased sleep fragmentation, more fragile sleep, reduced amount of deeper sleep (slow wave sleep), increased time spent awake throughout the night.^{2–5} While sleep pattern has been extensively investigated in young and older adults, less data are

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available for the oldest-old individuals (aged 85 years and over).⁴ due to the difficulty in recruiting large samples. In older adults, sleep duration seems to be correlated to good health and longevity. Tamakoshi et al.⁶ reported that a sleep duration at night of 7 h was associated with a lower mortality risk. In a study conducted on 3927 nonagenarians and 2794 centenarians of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). Gu et al.⁷ using self-reported sleep questionnaires, observed an association between poor sleep and physiological and psychosocial factors (i.e., daytime activities, family/social support). In the study by Gu et al., the observed sample of the oldest-old tended to sleep either shorter or longer than young elders. However, the quality of sleep, in octogenarians, nonagenarians, and centenarians did not differ much from young elders and resulted to be even better in the oldest-old sample when demographics, social, and health conditions were controlled for. These results are in line with those obtained from Tafaro et al^8 on a sample of 180 centenarians, reporting severe sleep problems only in 7.4% of the sample, and reinforcing the hypothesis that healthy elders experience satisfactory sleep quality. However, the above-mentioned results are based on selfreported questionnaires, although it has been suggested that questionnaires may not be the best sleep quality measure for elderly subjects, due to their reliance on cognitive capacity.⁹ Indeed, discrepancies between actigraphic measurements and self-reported sleep quality are reported in the literature for older adults.⁹ Considering that people older than 85 years represent the fastest-growing age group in all high-income countries,¹⁰ it appears of the utmost importance to more deeply explore the sleep characteristics of this particular population segment.

The aims of this study were: (i) to objectively investigate, using a wearable device, the sleep characteristics of a large community of oldest-old subjects living in the Mugello area (Italy); (ii) to assess whether there are significant differences in sleep parameters, measured using the wearable device, between self-reported 'good sleepers' and 'bad sleepers'; and (iii) to investigate the relationship between sleep parameters and cognitive status in this community-dwelling population.

MATERIAL AND METHODS Study population

Data presented in this work were collected in the framework of the 'Mugello study'. The 'Mugello study' is a cross-sectional survey of oldest-old subjects, conducted in the Mugello area (north-east of Florence, Italy).¹¹ In brief, 504 oldest-old (135 men/364 women) were administered at their homes/retirement homes a series of validated questionnaires on functional independence, physical activity level, quality of life, and falls and underwent instrumental examinations and blood withdrawal. Data on medical history and social, functional, and cognitive status were collected. Together with the above-mentioned data, those who agreed to participate in the Mugello study were asked to provide information about their quality of sleep and to wear an armband device 24 h/day and complete at least two consecutive nights of data collection. Subjects eligible for this research were those participants who provided complete information about their sleep quality and agreed to wear the armband device. Informed written consent was obtained from all the participants, before they were included in the study, in agreement with the principles of the Declaration of Helsinki on clinical research involving human beings and was approved by the Don Carlo Gnocchi Foundation Ethics Committee (Assembly 15 October 2010).

Outcome measures

All subjects underwent a cognitive evaluation through the Mini-Mental State Examination (MMSE).¹² The MMSE global score ranges between 0 and 30, with a lower score indicating more severe impairment. Since a score correction for educational level and age is not available for people aged over 85 years, the MMSE raw score was used in this analysis. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI).¹³ The study sample was divided into two groups according to the PSQI score. A global score greater than five was used to discriminate between good and poor sleepers.¹³

Armband

Objective estimation of sleep parameters was obtained using the SenseWear armband (BodyMedia Inc., USA). The armband is a device that combines information from different sensors such as an accelerometer, heat flux, galvanic skin response, and temperature sensors to provide minute-by-minute estimates of energy expenditure, metabolic physical activity, sleep-wake cycle, sleep quality, and efficiency in a free-living environment. The armband was placed over the subjects' triceps muscle, halfway between the acromion and the olecranon processes, according to the manufacturer's instructions.

The SenseWear armband estimation of sleep parameters has been validated in patients with obstructive sleep apnoea and controls against polysomnography.¹⁴ The standard factory-default algorithm was used for sleep interval detection. The algorithm uses average variations in body movements, differential and proportional changes in heat flux and skin temperature, and the galvanic skin response to score each 1-min time epoch as either asleep or awake.¹⁵ MATLAB R2011b (MathWorks, USA) customised algorithm was used to calculate the length of awake/asleep periods and average their values over recording time. The following sleep parameters were estimated: time spent in bed (TIB: time between inbed time and out of bed time), sleep end (the time the subject last woke up in the morning), total sleep time (TST: the total sum of the minutes scored sleeping from sleep onset to the sleep end); sleep efficiency (SE: the ratio of TST to TIB); sleep onset latency (SOL: the time lag between in-bed time and sleep onset); number and duration of awakenings after sleep onset; wakefulness after sleep onset (WASO: the time spent awake after initial sleep onset until sleep end), numbers and duration (average time slept) of naps. All parameters were calculated on a night-by-night basis and values obtained were averaged.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software (IBM SPSS Statistics, Version 27.0., IBM, Corp., Armonk, NY, USA). First, continuous variables, namely age, body mass index (BMI), education, MMSE total score, PSQI score, number of recording nights, percentage of worn time, TIB, TST, SE, SOL, numbers of awakenings, WASO, number of naps, and nap durations, were checked for normality using the Shapiro–Wilk test. Except for BMI and PSQI score which were described with their means and SDs, all variables did not present a normal distribution and were thus described with their median values and interquartile ranges (IQRs). Variables with a normal distribution were compared between the

groups of men/women, and PSQI < $5/PSQI \ge 5$ using the independent *t*-test. Data that did not follow a normal distribution and dichotomous variables were compared between the same groups using a Mann-Whitney U-test or a Chi-square test, respectively. In all analyses, a P-value < 0.05 was considered statistically significant. The study sample was then divided into four groups according to the observed MMSE raw score. Sociodemographic variables, use of drugs that might interfere with sleep guality/guantity, and sleep parameters were compared between the four groups using the Jonckheere-Terpstra test. Two-sided statistical significance was set at an alpha level of 0.05. Post hoc analysis was performed using pairwise comparisons and by applying the Bonferroni correction.

Those variables showing a statistically significant difference between the four groups in the previous analysis were introduced as potential confounding factors in an ordinal logistic regression model, to study the possible association between sleep parameters and cognitive function.

RESULTS

Among all subjects enrolled in the study (N = 504), 225 participants agreed to wear the armband device. Thirty-five subjects were unable or refused to complete at least 2 nights of data collection, while 12 had incomplete clinical data and were thus excluded from further analyses, yielding a data collection completion rate of 79.1% (n = 178). Those subjects that did not completed data collection (excluded) did not differ from included subjects with respect to gender (P = 0.378), age (P = 0.379), and education (P = 0.111). The only significant differences were found in the percentage of institutionalised people, 5.6% and 30.4%, respectively in the included and excluded group (P < 0.001) and in the MMSE raw score (P = 0.002). More details are provided in Table S1. The study group was characterised by a predominance of women (74.2%) and a median age of 92 years (IQR: 6 years). The baseline demographic and clinical characteristics of these participants are summarised in Table 1. Women had a lower educational level (median duration: 4 years vs 5 years, P = 0.002), showed a lower prevalence of pulmonary diseases (3.8% vs 17.4%, P = 0.005), and a lower MMSE score (24 vs 26, P = 0.022). Details on sleep

Table 1 Participants' characteristics and armband sleep parameters

	Total (N = 178)	Men (<i>n</i> = 46)	Women (<i>n</i> = 132)	Р
Age, years	92 [6]	91 [5]	92 [6]	0.119
BMI, kg/m ²	$\textbf{25.1} \pm \textbf{4.3}$	24.9 ± 3.4	25.2 ± 4.6	0.923
Education, years	4 [2]	5 [5]	4 [2]	0.00
Institutionalised, yes	10 (5.6%)	2 (4.3%)	8 (6.1%)	1.000
Cardiovascular diseases, yes	88 (49.4%)	29 (63.0%)	59 (44.7%)	0.03
Pulmonary diseases, yes	13 (7.3%)	8 (17.4%)	5 (3.8%)	0.00
Cerebrovascular disease, yes	29 (16.3%)	8 (17.4%)	21 (15.9%)	0.81
Dyslipidaemia, yes	21 (11.8%)	4 (8.7%)	17 (12.9%)	0.449
Dementia, yes	13 (7.3%)	2 (4.3%)	11 (8.3%)	0.519
Diabetes mellitus, yes	24 (13.5%)	5 (10.9%)	19 (14.4%)	0.54
Tumour, yes	26 (14.6%)	11 (23.9%)	15 (11.4%)	0.03
Drugs				
β-blockers, yes	24 (13.8%)	4 (8.7%)	20 (15.6%)	0.242
Benzodiazepines, yes	34 (19.2%)	5 (10.9%)	29 (22.1%)	0.09
Antidepressants, yes	32 (18.1%)	7 (15.2%)	25 (19.1%)	0.558
Antipsychotics, yes	10 (5.6%)	1 (2.2%)	9 (6.9%)	0.45
Steroids, yes	9 (5.1%)	4 (8.7%)	5 (3.8%)	0.24
MMSE total, score	22 [11]	26 [11]	22 [11]	0.02
PSQI, score	7.3 ± 4.1	7.2 ± 3.9	7.4 ± 4.2	0.59
<5	42 (23.6%)	11 (23.9%)	31 (23.5%)	0.95
≥5	136 (76.4%)	35 (76.1%)	101 (76.5%)	
Number of recording nights	5.0 [3.0]	4.5 [3.0]	5.0 [3.0]	0.770
Percentage of worn time	99.5 [3.0]	99.0 [4.0]	100.0 [3.0]	0.64
TIB, min	528.3 [135.7]	538.3 [130.1]	518.9 [137.1]	0.984
TST, min	426.6 [148.8]	453.1 [148.6]	423.4 [162.0]	0.742
SE, %	83.0 [13.0]	81.0 [16.0]	84.0 [11.0]	0.23
SOL, min	17.2 [21.7]	15.6 [15.2]	18.0 [23.8]	0.743
Numbers of awakenings	8.5 [4.4]	9.0 [5.1]	8.2 [4.5]	0.248
WASO, min	110.0 [83.6]	109.7 [84.3]	110.0 [84.5]	0.87
Number of naps	3.0 [3.0]	4.0 [3.0]	3.0 [3.0]	0.96
Nap duration, min	35.5 [27.7]	31.9 [20.6]	36.0 [33.3]	0.320

Note: Parameters characterised by a normal distribution (BMI, PSQI) are expressed as mean \pm SD, parameters with a non-normal distribution (age, education number of recording nights, percentage of worn time, TIB, TST, SE, SOL, numbers of awakenings, WASO, number of naps, nap's duration) as median [interquartile range], dichotomous parameters as number of subjects (*n*) and percentage (%). Bold highlights variables statistically significant (P < 0.05). BMI, body mass index; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; TIB, time in bed; TST, total sleep time; SE, sleep efficiency; SOL, sleep on latency; WASO, wakefulness after sleep onset.

parameters estimated in men, women, and the entire study sample are also reported in Table 1. Participants were recorded for a median time of 5 days (2 to 10 days). The recorded median TIB was close to 9 h with a SE of 83%. Since no significant differences (P > 0.05) were observed due to gender, data were pooled in subsequent analyses.

According to the PSQI results, 42 participants (23.6%) were classified as good sleepers (PSQI < 5) and 136 (76.4%) as poor sleepers (PSQI > 5). Results of the comparison between self-reported sleep quality and sleep parameters estimated using the SenseWear armband are given in Table 2. The latter did not show any significant difference between poor and good sleepers, identified according to their PSQI score.

The results of the Jonckheere–Terpstra test performed to evaluate differences in sociodemographic variables, use of drugs, and sleep parameters among subjects with different levels of cognitive

Table 2 Armband sleep	parameters in	'good'	and	'poor'	sleepers,
according to PSQI					

	PSQI < 5 (n = 42)	PSQI≥5 (n = 136)	Р
Number of recording nights	5.0 [2.0]	5.0 [3.0]	0.935
Percentage of worn time	99.0 [5.0]	100.0 [3.0]	0.302
TIB, min	510.8 [146.2]	529.1 [134.2]	0.734
TST, min	432.2 [145.6]	426.6 [152.1]	0.502
SE, %	82.0 [13.0]	84.0 [12.0]	0.194
SOL, min	20.9 [29.3]	16.4 [20.4]	0.438
Numbers of wake-ups	8.4 [5.1]	8.5 [4.1]	0.311
WASO, min	108.2 [97.5]	110.7 [84.2]	0.629
Numbers of naps	3.0 [4.0]	3.0 [3.0]	0.665
Nap duration, min	33.0 [23.0]	36.0 [29.7]	0.712

Note: Data are presented as median [interquartile range]. PSQI, Pittsburgh Sleep Quality Index; SE, sleep efficiency; SOL, sleep on latency; TIB, time in bed; TST, total sleep time; WASO, wakefulness after sleep onset.

	MMSE 0–10 (n = 24)	MMSE 11–17 (n = 33)	MMSE 18–23 (n = 38)	MMSE ≥24 (<i>n</i> = 83)	Р
Gender, female	21 (87.5%)	23 (69.7%)	33 (86.8%)	55 (66.3%)	0.036‡
Age, years	98 [5]	94 [5]	92 [5]*,**	91 [4]*,**	<0.001
Education, years	3 [2]	3 [3]	4 [3]	5 [2]**,***	<0.001
Use of drugs†	9 (39.1%)	14 (42.4%)	16 (42.1%)	30 (36.1%)	0.896
Number of nights	5.0 [2.0]	5.0 [3.0]	4.0 [3.0]	5.0 [3.0]	0.902
Percentage of worn time	98.0 [9.0]	100.0 [3.0]	100.0 [3.0]	99.0 [3.0]	0.506
TIB, min	595.0 [171.1]	556.8 [172.5]	555.3 [133.4]	505.3 [124.6]*	0.001
TST, min	489.0 [161.1]	431.0 [199.2]	444.0 [148.7]	421.0 [127.4]	0.152
SE, %	80.5 [11.0]	80.0 [15.0]	84.0 [6.0]	85.0 [12.0]	0.019
SOL, min	32.3 [39.9]	16.8 [20.3]*	15.6 [31.2]*	15.1 [14.8]*	0.037
Numbers of wake-ups	9.3 [6.0]	9.0 [4.3]	8.0 [4.0]	8.5 [4.5]	0.613
WASO, min	136.0 [97.0]	144.1 [113.6]	98.4 [79.0]	107.0 [74.8]	0.004
Numbers of naps	4.0 [3.0]	4.5 [3.0]	3.0 [2.0]**	3.0 [3.0]**	0.016
Nap duration, min	36.2 [44.0]	36.3 [23.6]	36.3 [29.0]	35.0 [26.3]	0.786

Table 3	Armhand sleen	narameters in	narticinants	stratified by MMSE	
I able 3	Annuanu sieep	parameters in	participarits	Stratilieu by Wilvioe	

Note: Data are presented as median [interquartile range]. Bold highlights variables statistically significant (P < 0.05). MMSE, Mini-Mental State Examination; TIB, time in bed; TST, total sleep time; SE, sleep efficiency; SOL, sleep on latency; WASO, wakefulness after sleep onset. [†]At least one drug among β -blockers, benzodiazepines, antidepressants, and steroids. [‡]Not significant after Bonferroni correction. *P < 0.05 vs MMSE 0–10; **P < 0.05 vs MMSE 11–17; ***P < 0.05 vs MMSE 18–23.

performance are given in Table 3. Age, education, TIB, SOL, and the number of naps resulted to be significantly different in subjects assigned to different cognitive groups. Subjects with a higher level of cognitive functioning were younger (median age 92 and 91 years in the groups with MMSE 18–23 and \geq 24, compared to median age 97.5 and 94 years in the groups with MMSE 0-10 and 11-17, respectively; P < 0.001), with a higher level of education (5 years of education in the group with MMSE ≥24 vs 3 to 4 years of education reported in the groups with MMSE <24; P < 0.001), spent less time in bed (median time 505.3 min in the group with MMSE ≥24 vs 555.3 to 595.0 min recorded in the groups with MMSE <24; P = 0.001), had a shorter SOL (32.3 min in the group with MMSE 0-10 vs 15.1 to 16.8 min recorded in the groups with MMSE >10; P = 0.037) and had fewer diurnal naps (median count three in the groups with MMSE 18–23 and ≥24 vs four and 4.5 in the groups with MMSE 0-10 and MMSE 11-17, respectively;

Table 4 Orc	linal logistic	rearession	output
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P = 0.016). In particular, SOL remained significantly associated with the MMSE score even when adjusted for age and education (details on the results from the ordinal logistic regression analysis are given in Table 4), with an expected decrease in SOL for increasing levels of cognitive performance (B = -0.014, P = 0.004).

DISCUSSION

This study presents an objective characterisation of sleep in a large sample of oldest-old individuals underlining a lack of consistency between objective measures of sleep parameters and reported sleep quality. TIB and TST measured in this study were in line with previous actigraphic measurements, conducted by Fung *et al.*¹⁶ in a sample of 826 adults aged 87.6 \pm 2.9 years (TIB 531.4 \pm 74.5, TST 426.7 \pm 81.9) and by Kim *et al.*¹⁷ in a sample of 207 adults aged 80–95 (TST 408.2 \pm 66.7). TST values measured in our sample were higher

			95% confid	ence interval	
	В	SE	Lower bound	Upper bound	P-value
Age, years	-0.202	0.054	-0.308	-0.095	0.000
Education, years	0.219	0.077	0.068	0.369	0.004
TIB, min	-0.002	0.002	-0.005	0.002	0.336
SOL, min	-0.014	0.005	-0.024	-0.005	0.004
Number of naps	-0.135	0.081	-0.294	0.023	0.095

Note: Dependent variable: MMSE groups, according to Table 3. Nagelkerke R^2 : 0.31; P < 0.001. Bold highlights variables statistically significant (P < 0.05). Abbreviations: TIB, time in bed; SOL, sleep on latency.

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compared to a recently published meta-analysis reporting literature data on young-old (70–80 years; TST: 6.80 h) and old (70–80 years; TST: 6.35 h) groups.¹⁸ Our participants showed a SE lower than that reported by Mazzotti (89.7 ± 4.3) in a small sample of 10 oldest-old individuals aged 85–105 years (18) and later by Kim and colleagues (90.5 ± 4.9).¹⁷ Literature data on young-old and old populations report a SE of 85.36 and 86.86 for the two groups, respectively.¹⁸ Different from previous actigraphic estimations, a higher SOL (11.8 ± 4.5 (18)), a lower number of awakenings (11.1 ± 4.9 (16)), and higher values for the WASO parameter (73.6 ± 47.8 (15), 41.3 ± 22.2 (16), 52.6 ± 15.2¹⁵), were measured in our sample of nonagenarians.

Sleep structure has been previously assessed also by Wauquier *et al.*¹⁹ in 14 healthy individuals aged 88–102 years, using polysomnography. Their main findings were the gender differences in sleep parameters which were not confirmed in this study.

Participants' groups based on PSQI scores did not differ from each other on sleep parameters, measured by actigraphy. This is consistent with previous studies conducted on younger groups, which have shown weak or inconsistent associations between the PSQI and the actigraphic estimations.^{9,20} In particular, Landry and colleagues⁹ observed, in a sample of adults aged 55 years and over, that those individuals categorised as poor sleepers based on the PSQI were equally likely to be classified as poor or good sleepers based on the actigraphic data. Similar results emerged when looking at individuals categorised as good sleepers (χ^2 reported from the cross-tabulation $\chi^2 = 0.195$, P = 0.907).

In our study group, higher sleep latency was consistently related to poorer cognition, whereas the association with other sleep parameters did not remain significant when the analysis was adjusted for age and education. While sleep is critical for optimal cognitive function at all ages, there is a growing interest in the sleep-cognition relationship in the elderly. However, among previous studies that have examined the association between sleep parameters and cognition only a few have focused on the oldest-old population. Sabeti *et al.*²¹ in a group of 144 nonagenarians and centenarians found a significant association between sleep quantity and global cognition, with a long sleep (>8 h) associated with a poor MMSE score; different from this study, a selfadministered questionnaire was used to obtain quantitative and qualitative sleep parameters, and measures of sleep fragmentation, SE, and napping were not available for comparison. Results from our study are in line with those reported by Chang-Quan *et al.*²² who found lower cognitive function scores (evaluated using the MMSE) to be significantly associated with longer sleep latency, but not with sleep duration, among 660 individuals aged 90 years and above. In addition, they observed a significant correlation between poor sleep quality and poor SE with poor cognitive function. However, as sleep parameters were assessed using the PSQI, caution should be used with interpretation, as discussed above.

This study presents some limitations. The crosssectional design precludes drawing firm conclusions regarding the causal direction of the relationship between sleep features and cognitive status. In our sample, the comparison between objective and subjective sleep assessment did not appear to be affected by the number of nights evaluated (data shown in Supplementary Materials, Table S2). However, due to the duration of monitoring, relying on a median of 5 nights observation, failure to account for some pattern of sleep or measurements of sleep that deviated from normal cannot be completely excluded. Further studies with longer duration of monitoring are warranted to confirm the results obtained in this study. Nevertheless, this work has several strengths. First of all, it includes a large sample of nonagenarians; the only previous quantitative study involving a large sample of nonagenarians was the one conducted by Fung et al.¹⁶ which included only women. Second, almost the entire study sample (93%) lived at home, thus it was likely to be most representative of the oldest-old population. With the broader aim to provide insights for reconsidering our indications for rehabilitation in this age group and for designing rehabilitation programs specifically tailored for nonagenarians, which is the main purpose of the Mugello study, we believe that an objective measurement of sleep parameters should be used for a more accurate and unbiased evaluation in this population.

CONCLUSIONS

We described the sleep profile, investigated using both a subjective and objective evaluation, in a large sample of nonagenarians. Actigraphic measurements revealed that subjects with the worst cognitive status were more prone to increased SOL. No significant difference in sleep parameters estimated using the SenseWear armband were found between poor and good sleepers, classified according to their PSQI score. Our findings suggest the need to introduce objective measures, collected through easy-to-use tools (e.g., actigraphy) when investigating sleep quality in older adults.

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DISCLOSURE

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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APPENDIX S1: Supplementary Information