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Effects of Sleep-Disordered Breathing on Daytime Brain Activity in Community-Dwelling Older Adults

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Abstract

Introduction Sleep-disordered breathing (SDB) is associated with an increased risk of cardiovascular diseases. The present study aimed to examine the influence of SDB on daytime brain activity in the community-dwelling older adults.

Material and Methods Eighty one consecutive volunteers aged 60 years or older (mean age 70.5 ± 4.8 years) participated in the present study. Daytime brain activity was assessed by measuring the peak cortical oxygenated hemoglobin (OxyHb) levels and area under the near-infrared spectroscopy (NIRS) curve. The respiratory event index (REI) and 3% oxygen desaturation index (3%ODI) were evaluated using a home sleep-apnea test.

Results The peak OxyHb and area under the NIRS curve were significantly lower in the participants with REI $\geq$ 15/h than those with REI $<$ 15/h. The body mass index (BMI), REI, 3%ODI, and Epworth sleepiness scale (ESS) scores were significantly correlated with peak OxyHb levels (BMI: r = -0.202, p = 0.035; REI: r = -0.307, p = 0.003; 3%ODI: r = -0.321, p = 0.002; and ESS score: r = -0.287, p = 0.005). Also, the BMI, REI, and 3%ODI were significantly correlated with the area under the NIRS curve (BMI: r = -0.306, p = 0.002; REI: r = -0.326, p = 0.002; and 3%ODI: r = -0.322, p = 0.002), and BMI was a significant factor associated with the area under the NIRS curve.

Conclusions Brain activity during wakefulness was associated with severities of SDB and obesity. A simple NIRS may yield unique information for characterizing the decline in daytime brain activity of the community-dwelling older adults.

Keywords
- brain activity
- sleep-disordered breathing
- daytime sleepiness
- older adults
- near-infrared spectroscopy

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Introduction

The prevalence of sleep-disordered breathing (SDB) was estimated as high as 20 to 40% in the geriatric population, and it was expected to increase with the population's aging.[1,2] This disorder leads to a potential risk of cerebrovascular and cardiovascular diseases,[3] and might lead to hypoxemia, pressure swings of the thorax, frequent arousals, sleep fragmentation, and activation of the sympathetic nervous system.[4–6] Chronic intermittent episodes of hypoxia could induce oxidative stress, inflammation of the whole body, and, possibly, degeneration of the central nervous system.[7] Moreover, quality of life was impaired by the coexisting SDB, which decreased mental/physical activity.[8] Therefore, an early detection and appropriate treatment of SDB have beneficial effects on the cognitive function of older adults.

According to the previous studies using the functional magnetic resonance imaging (fMRI), the broad functional connectivity was reduced among the frontal, cingulate, temporal, parietal, occipital, and cerebellar regions of the brain in patients with SDB.[9] Near-infrared spectroscopy (NIRS) with high temporal resolution is a noninvasive method for assessing the brain activity, which measures the relative changes in oxygenated hemoglobin (OxyHb) of the cerebral cortex.[10] In previous studies, we have reported that short sleep duration had a negative impact on the cortical oxygenation during a word fluency task evaluated using the NIRS.[11,12] Since the target population of the present study is community-dwelling older adults, we have utilized the NIRS to measure brain activity, as it is simpler, less expensive, and less invasive than fMRI.

The present study aimed to clarify the relationship between brain activity and SDB in the target population.

Materials and Methods

Participants

A total of 81 consecutive volunteers aged $\geq$ 60 years (51 men, 30 women; mean age 70.5 $\pm$ 4.8 years) were enrolled in the present study. The participants had no history of myocardial infarction, angina pectoris, heart failure, cerebral infarction, cerebral hemorrhage, chronic obstructive pulmonary disease, psychiatric disorders, or the use of antidepressants, benzodiazepines, or current medications for sleep problems. We used a questionnaire to collect the following data: age; body mass index (BMI); smoking status; alcohol intake; history of hypertension, diabetes mellitus, and/or hyperlipidemia; and current use of medications. Active smokers were defined as the participants who were currently smoking or those who had quit smoking for $<$ 4 years prior to the study.[13] Alcohol intake was defined as an individual who drank regularly.[14] Systolic (SBP) and diastolic blood pressure (DBP) were measured using a plethysmograph (BP-203RPEIII, Omron Colin Co., Ltd., Tokyo, Japan) prior to the NIRS measurements. The participants with SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg, or those undergoing antihypertensive therapy, were considered to have hypertension.[15] Diabetes mellitus and hyperlipidemia were defined by the use of oral hypoglycemic and lipid-lowering agents, respectively.

The protocol for the present study was approved by the Ethics Committee of the Chubu University (number 270098). After explaining the nature of the study and the procedures involved, the written informed consents were obtained from all participants.

Questionnaires

Epworth Sleepiness Scale (ESS)

Subjective excessive daytime sleepiness was evaluated using the Epworth sleepiness scale (ESS).[16] In this questionnaire, the participants used a four-point scale to rate their chances of dozing off in eight different situations, all of which could be encountered in daily life. The total ESS score was the sum of all responses, ranging from 0 to 24 points.

Pittsburgh Sleep Quality Index

Subjective sleep quality over the prior month was assessed using the Pittsburgh sleep quality index (PSQI),[17] which contained 19 items in 7 component domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The 19 self-rated items were combined to form 7 component scores, each of which had a range from 0 to 3 points. In all cases, a score of 0 indicated no difficulty, while a score of 3 indicated severe difficulty. The 7 component scores were then totaled to yield a global PSQI score, ranging from 0 to 21 points.

Near-Infrared Spectroscopy (NIRS) during Word Fluency Task

Relative concentrations of OxyHb were measured using the 2-channel NIRS recorder (HOT121B; Hitachi High-Technologies Co., Tokyo, Japan), while the participant underwent a word fluency task. The NIRS probes (3 cm distance between the emitter and detector probes) were placed on the left and right frontal areas, including Fp1 and Fp2, according to the international 10-20 electroencephalography system. The absorption of near-infrared light was measured with a temporal resolution of 0.1 seconds.

The word frequency task was performed as previously described.[18] In brief, the 30-second pretask involved repeating the vowels 'a, i, u, e, o', and then speaking out any random words starting with the three initial Japanese syllables in 20 seconds each. This was followed by a post-task, which again involved repeating the vowels, and a 70-second post-task (►**Fig. 1**). The values recorded from both channels in the frontal area were then averaged to obtain the results.

Peak OxyHb was measured during the word fluency task. The area under the NIRS curve was also measured using the trapezium rule, which approximated this area, as described by the function f(x).

Home Sleep Apnea Test (HSAT)

The participants were screened for SDB using a portable device (SAS-2100, Nihon Kohden Corp., Tokyo, Japan), in

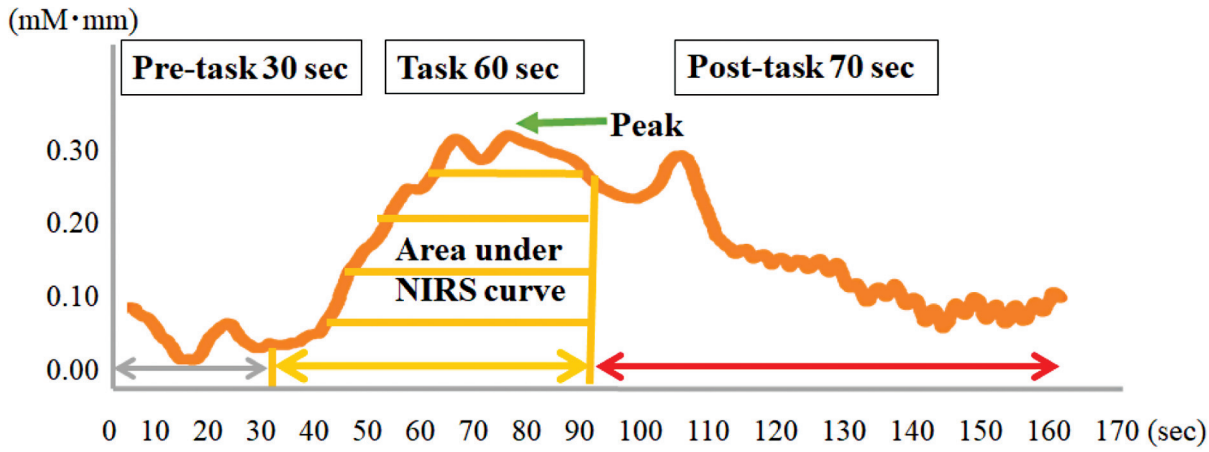

Fig. 1 The NIRS curve of a representative case. During the word fluency task, the area under the NIRS curve was measured using the trapezium rule, which approximated that area to measure the integral. Peak OxyHb was also measured.

Table 1 Baseline characteristics and sleep/NIRS parameters by gender

	Total ($n = 81$)	Men ($n = 51$)	Women ($n = 30$)	*p*-value
Demographics				
Age (years)	70.5 ± 4.8	70.1 ± 4.1	71.2 ± 5.9	0.377
Height (cm)	161.0 ± 8.6	165.6 ± 6.7	153.2 ± 5.1	< 0.001
Weight (kg)	60.0 ± 10.4	64.2 ± 9.5	53.0 ± 8.1	< 0.001
BMI (kg/m^2)	23.0 ± 3.1	23.2 ± 3.2	22.8 ± 2.9	0.591
SBP (mmHg)	141.5 ± 15.4	142.6 ± 13.9	139.6 ± 17.6	0.399
DBP (mmHg)	83.6 ± 9.1	84.9 ± 8.4	81.4 ± 9.9	0.099
Risk factors				
Smoking (%)	33.3	49.0	6.7	< 0.001
Alcohol intake (%)	59.2	74.5	33.3	< 0.001
Hypertension (%)	54.3	54.9	53.3	0.891
Diabetes mellitus (%)	4.9	3.9	6.7	0.474
Hyperlipidemia (%)	16.0	7.8	30.0	0.011
Sleep parameters				
Questionnaires				
Sleep duration (min)	428.3 ± 73.4	434.2 ± 79.8	418.4 ± 60.9	0.354
ESS score	5.6 ± 3.9	5.5 ± 3.9	5.9 ± 3.9	0.661
PSQI score	5.5 ± 2.9	5.5 ± 3.1	5.5 ± 2.6	0.988
Home sleep apnea test				
REI (/h)	9.7 ± 9.5	10.3 ± 10.1	8.6 ± 8.2	0.425
3%ODI (/h)	14.1 ± 11.1	14.9 ± 11.7	12.8 ± 10.1	0.402
Minimum SpO_2 (%)	86.2 ± 5.2	86.3 ± 5.2	86.2 ± 5.3	0.986
NIRS parameters				
Peak OxyHb (mM · mm)	0.316 ± 0.260	0.302 ± 0.255	0.339 ± 0.270	0.549
Area under the NIRS curve	102.6 ± 144.5	78.9 ± 135.3	143.0 ± 152.9	0.053

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; ESS, Epworth sleepiness scale; NIRS, near-infrared spectroscopy; ODI, oxygen desaturation index; OxyHb, oxygenated hemoglobin; PSQI, Pittsburgh sleep quality index; REI, respiratory event index; SBP, systolic blood pressure.
Notes: Data are expressed as mean ± SD.

which a nasal pressure sensor and a pulse oximeter were used to record airflow, pulse wave, and oxygen saturation (SpO_2), respectively. They were instructed on how to wear and use the device at home. We calculated the respiratory event index (REI) as the total number of apnea and hypopnea events occurring per hour for the total duration of the recording time. The number of events per hour with oxygen desaturation $\geq$ 3% (3% oxygen desaturation index: 3%ODI). The minimum SpO_2 values were also evaluated.

Statistical Analyses

All data are presented as mean $\pm$ standard deviation (SD). We compared data on the smoking status, alcohol intake, hypertension, diabetes mellitus, hyperlipidemia, medication use, ESS score, PSQI score, HSAT results, and NIRS parameters between the groups (men vs. women, REI $\geq$ 15/h vs. $<$ 15/h,[19,20] and 3% ODI $\geq$ 15/h vs. $<$ 15/h) using the chi-squared test or non-paired *t*-test. Based on the results of the preliminary test, we calculated the number of subjects required to verify this study and the power. Pearson correlation analysis was performed to evaluate the relationships between the sleep parameters and NIRS.

Moreover, a multiple linear regression analysis was performed to examine the association of NIRS parameters (peak OxyHb and area under the NIRS curve) with age, BMI, sex, smoking status, sleep duration, REI, 3%ODI, ESS score, and PSQI score. Significant factors were obtained from the correlation analysis. Probability values lower than 0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package Social Sciences (SPSS, IBM Corporation, Armonk, NY, USA) version 25.0.

Results

The baseline characteristics of the study participants are shown in ►**Table 1**. Men had a significantly higher prevalence of smoking and alcohol use, and a significantly lower incidence of hyperlipidemia than women. There were,

Table 2 Baseline characteristics and sleep/NIRS parameters by respiratory event index

	REI $<$ 15/h (n = 61)	REI $\geq$ 15/h (n = 20)	*p*-value
Demographics			
Age (years)	70.8 $\pm$ 4.8	69.8 $\pm$ 4.8	0.445
Men (%)	60.7	70.0	0.453
Height (cm)	160.5 $\pm$ 8.6	162.4 $\pm$ 8.5	0.396
Weight (kg)	57.3 $\pm$ 8.5	68.4 $\pm$ 11.6	$<$ 0.001
BMI (kg/m^2)	22.2 $\pm$ 2.5	25.4 $\pm$ 3.7	0.002
SBP (mmHg)	140.1 $\pm$ 16.0	145.7 $\pm$ 12.6	0.158
DBP (mmHg)	82.7 $\pm$ 9.5	86.2 $\pm$ 7.2	0.134
Risk factors			
Smoking (%)	29.5	45.0	0.202
Alcohol intake (%)	62.3	50.0	0.331
Hypertension (%)	54.1	55.0	0.944
Diabetes mellitus (%)	6.6	0.0	0.314
Hyperlipidemia (%)	18.0	10.0	0.322
Sleep parameters			
Questionnaires			
Sleep duration (min)	426.5 $\pm$ 76.3	433.9 $\pm$ 65.0	0.697
ESS score	5.0 $\pm$ 3.5	7.5 $\pm$ 4.5	0.014
PSQI score	5.5 $\pm$ 2.8	5.5 $\pm$ 3.3	0.991
Home sleep apnea test			
3%ODI (/h)	8.9 $\pm$ 5.4	30.1 $\pm$ 8.5	$<$ 0.001
Minimum SpO_2 (%)	87.6 $\pm$ 4.6	82.1 $\pm$ 4.6	$<$ 0.001
NIRS parameters			
Peak OxyHb (mM $\cdot$ mm)	0.357 $\pm$ 0.280	0.191 $\pm$ 0.124	$<$ 0.001
Area under the NIRS curve	123.1 $\pm$ 149.0	40.3 $\pm$ 111.6	0.025

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; ESS, Epworth sleepiness scale; NIRS, near-infrared spectroscopy; ODI, oxygen desaturation index; OxyHb, oxygenated hemoglobin; PSQI, Pittsburgh sleep quality index; REI, respiratory event index; SBP, systolic blood pressure.
Notes: Data are expressed as mean $\pm$ SD.

however, no significant differences in the sleep and NIRS parameters between men and women.

Body weight, BMI, and ESS score were significantly higher in the participants with REI $\geq$ 15/h than those with REI $<$ 15/h. Peak OxyHb and area under the NIRS curve significantly decreased in the participants with REI $\geq$ 15/h than those with REI $<$ 15/h (►**Table 2**). The number of subjects required to verify this study was 32 cases in one group and 64 cases in the two groups with the power of 77.6%.

Body weight, BMI, and ESS score significantly increased in participants with 3% ODI $\geq$ 15/h than those with 3% ODI $<$ 15/h. Peak OxyHb, and the area under the NIRS curve significantly decreased in the participants with 3%ODI $\geq$ 15/h than those with 3% ODI $<$ 15/h (►**Table 3**). The number of subjects required to verify this study was 32 cases in one group and 64 cases in the two groups with the power of 86.7%.

The BMI (r = -0.202, p = 0.035), REI (r = -0.307, p = 0.003), 3%ODI (r = -0.321, p = 0.002), and ESS score (r = -0.287, p = 0.005) were significantly correlated with peak OxyHb levels. Also, the BMI (r = -0.306, p = 0.003), REI (r = -0.326, p = 0.002), and 3%ODI (r = -0.322, p = 0.002) were significantly correlated with the area under the NIRS curve. Multiple regression analysis revealed that BMI was a significant factor for the area under the NIRS curve (β = -0.247, p = 0.044) (►**Table 4**).

Discussion

We found that the peak OxyHb and area under the NIRS curve were decreased with increasing REI and 3%ODI, and that increases in the ESS score and BMI were associated with the REI and 3%ODI. These results suggest that SDB may play a significant role in the decrease of daytime brain activity of community-dwelling older adults.

A previous fMRI study demonstrated that brain activity decreased significantly in the 24 patients with SDB than in the 24 healthy volunteers,[21] which seemed consistent with the findings of our present study. From a methodological

Table 3 Baseline characteristics and sleep/NIRS parameters by 3% oxygen desaturation index

	3%ODI $<$ 15/h (n = 52)	3%ODI $\geq$ 15/h (n = 29)	p-value
Demographics			
Age (years)	70.9 ± 4.9	69.8 ± 4.7	0.313
Men (%)	59.6	69.0	0.403
Height (cm)	160.6 ± 7.9	161.6 ± 9.7	0.620
Weight (kg)	57.0 ± 8.4	65.6 ± 11.6	$<$ 0.001
BMI (kg/m2)	22.1 ± 2.5	24.7 ± 3.7	$<$ 0.001
SBP (mmHg)	139.7 ± 17.0	144.7 ± 11.5	0.161
DBP (mmHg)	82.3 ± 9.9	85.9 ± 7.1	0.088
Risk factors			
Smoking (%)	28.8	41.4	0.251
Alcohol intake (%)	59.6	58.6	0.930
Hypertension (%)	44.8	54.3	0.200
Diabetes mellitus (%)	5.8	3.4	0.548
Hyperlipidemia (%)	21.2	6.9	0.083
Sleep parameters			
Questionnaires			
Sleep duration (min)	427.0 ± 72.3	430.8 ± 76.4	0.822
ESS score	4.7 ± 3.6	7.2 ± 4.0	0.005
PSQI score	5.3 ± 2.6	5.9 ± 3.4	0.312
Home sleep apnea test			
REI (/h)	4.1 ± 2.9	19.6 ± 8.9	$<$ 0.001
Minimum SpO_2 (%)	88.3 ± 4.4	82.6 ± 4.5	$<$ 0.001
NIRS parameters			
Peak OxyHb (mM · mm)	0.378 ± 0.295	0.204 ± 0.119	$<$ 0.001
Area under the NIRS curve	135.1 ± 154.8	44.4 ± 102.9	0.006

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; ESS, Epworth sleepiness scale; NIRS, near-infrared spectroscopy; ODI, oxygen desaturation index; OxyHb, oxygenated hemoglobin; PSQI, Pittsburgh sleep quality index; REI, respiratory event index; SBP, systolic blood pressure.
Notes: Data are expressed as mean ± SD.

Table 4 Relationship between NIRS parameters and baseline/sleep parameters.

	Simple correlation analysis		Multiple regression analysis		Simple correlation analysis		Multiple regression analysis	
	r	*p*-value	β	*p*-value	*r*	*p*-value	β	*p*-value
	Peak OxyHb				Area under the NIRS curve			
Age	-0.121	0.141	-0.182	0.115	-0.064	0.286	-0.155	0.168
BMI	-0.202	0.035	-0.104	0.402	-0.306	0.003	-0.247	0.044
Sex			-0.023	0.850		0.027	-0.121	0.306
Smoking			-0.115	0.361		0.008	-0.181	0.143
Sleep duration	-0.011	0.460	0.003	0.980	-0.124	0.135	-0.061	0.585
REI	-0.307	0.003	0.265	0.559	-0.326	0.002	-0.079	0.858
3%ODI	-0.321	0.002	-0.458	0.313	-0.322	0.002	-0.079	0.859
ESS score	-0.287	0.005	-0.216	0.066	-0.148	0.094	-0.064	0.574
PSQI score	-0.081	0.237	-0.006	0.956	-0.016	0.444	0.033	0.770

Abbreviations: BMI, body mass index; ESS, Epworth sleepiness scale; NIRS, near-infrared spectroscopy; ODI, oxygen desaturation index; OxyHb, oxygenated hemoglobin; PSQI, Pittsburgh sleep quality index; REI, respiratory event index.

viewpoint, the NIRS was a simple technology for assessing daytime brain activity through OxyHb of the cerebral cortex. In contrast, the fMRI was time-consuming and expensive,[10] making it difficult to assess the brain's neural function in community-dwelling older adults. Our previous NIRS study demonstrated that the cortical OxyHb response was blunted during word fluency tasks, which was associated with the short sleep duration in elderly volunteers.[22] This test, with its methodological and financial advantages over fMRI, could provide a novel insight into the brain activity of community-dwelling older adults.

Increases in REI and 3%ODI were found to be associated with an increase in the ESS score. Intermittent episodes of hypoxia and frequent arousals during sleep in patients with SDB could cause the symptoms of excessive daytime sleepiness, presumably.[23] For example, we previously showed that the arousal index was the most reliable predictor for the occurrence of automobile accidents, and that their incidence, near-misses, as well as scores of daytime sleepiness, were significantly correlated with the severity of nocturnal hypoxemia.[24] Moreover, we revealed that sleep fragmentation due to SDB led to an augmented sympathetic nerve activity during nighttime sleep.[5,6] Therefore, the symptoms of excessive daytime sleepiness can be attributed to the impaired brain activity during daytime wakefulness.

Sleep disturbances are common in aging and there is an increase in related disorders in pathological aging. These disturbances are characterized by decreased sleep duration, quality, and efficiency, and increased sleep fragmentation.[25,26] However, in our study, the peak OxyHb and area under the NIRS curve were not correlated with the PSQI score. In a previous study, we showed that a long sleep time and an irregular sleep–wake rhythm could have adverse effects on executive function and working memory in older people.[27] Hence, it might be difficult to evaluate the sleep problems associated with brain activity in older adults using PSQI alone. Mecca et al. demonstrated that there was no association between sleep disturbance and impaired cognitive functioning.[28] Kyle et al. reported higher cognitive functioning in a large sample of participants with insomnia.[29] These previous reports seem to support our findings.

In the present study, we showed that an increase in BMI was associated with an increase in REI and 3%ODI, and that BMI was a significant independent factor for the area under the NIRS curve. These results suggest that obesity might affect the occurrences of SDB and oxygen desaturation in the cerebral cortex, the latter of which was noted in the word frequency task during daytime wakefulness. A cohort study of men and women with a mean-age of 62 years reported a higher probability of association between gaining body weight and development of SDB.[30] Regarding this role, a previous study reported that apnea and hypopnea indices had worse results on patients with enhanced esophageal pressure, oxygen desaturation, and severity of obesity.[31] Studies have also shown that obesity can cause neuroinflammation, insulin resistance, and mitochondrial perturbations in the brain, which might impair cognitive function.[32] Thus, SDB aggravates oxygen desaturation during nighttime sleep in moderate to severe obesity, which in turn could jeopardize the reduced brain activity during daytime wakefulness.

There are two limitations of this study. First, neuroimaging techniques such as the fMRI and positron emission tomography could detect morphological changes in the cerebral vasculature,[33] whereas the NIRS was limited to OxyHb changes on the cortical surface. Second, the number of participants was relatively small, but the number of necessary subjects was satisfied at 81 subjects, considering the power. Therefore, to clarify the effects of SDB on the daytime brain activity, an intervention study encompassing a large population is necessary in the future.

Conclusions

We found that SDB with symptomatic daytime sleepiness adversely affected brain activity. The simple NIRS should

prove valuable for determining the decline in daytime brain activity and for detecting SDB in community-dwelling older adults.

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Conflict of Interests
The authors have no conflict of interests to declare.

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