



# Obstructive sleep apnea during rapid eye movement sleep and cognitive performance in adults

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## ARTICLE INFO

### Keywords:

OSA  
REM sleep  
Cognition  
Elderly people

## ABSTRACT

**Study objectives:** Obstructive sleep apnea (OSA) during rapid eye movement (REM) sleep is often characterized with more frequent and lengthy breathing events and greater oxygen desaturation than during other sleep stages. Current evidence suggests an association between OSA and cognitive decline, however whether OSA during REM sleep plays a vital role in this link is understudied.

**Methods:** A cross-sectional sample of 728 men and women (aged  $59.1 \pm 11.3$  years) underwent a full night polysomnography for determining apnea-hypopnea index (AHI) and sleep stages. Trail Making Test (TMT) part A and B were conducted during the following day for assessing participants' cognitive function. Linear regression analyses were performed to test the possible association between AHI and AHI during REM sleep with TMT-A and B results. Similar analyses were carried out in a subsample involving participants aged  $\geq 60$  years with  $\geq 30$  min of REM sleep ( $n = 356$ ).

**Results:** Despite a slight difference in TMT-B between participants with and without OSA (AHI  $\geq 5$  vs AHI  $< 5$ ,  $\beta$ -coefficient: 4.83, 95 % CI: [-9.44, -0.22],  $P = 0.040$ ), no other association between AHI or REM-AHI and TMT results were found in the full sample. In older participants (aged  $\geq 60$  years), a REM-AHI  $\geq 5$  events/hour was associated with longer time taken to finish TMT-A (vs REM-AHI  $< 5$  events/hour, 3.93, [0.96, 6.90],  $P = 0.010$ ). There was no association between REM-AHI and time taken to finish TMT-B in older participants.

**Conclusions:** The results indicate that OSA during REM sleep may be of particular concern for attention-related cognitive function in older adults.

## 1. Statement of significance

The study explored the relationship between obstructive sleep apnea (OSA) and cognitive function, specifically focusing on apnea-hypopnea index (AHI) during REM sleep. Among individuals aged 60 and above, AHI during REM sleep was associated with worse executive function and attention. This association was not observed with total AHI, highlighting the possible impact of REM sleep on cognition in OSA. The study indicates that OSA during REM sleep may have a greater negative effect on cognitive function compared to non-REM sleep. Clinicians may consider assessing AHI during REM sleep when evaluating cognitive function in individuals with OSA.

## 2. Introduction

Sufficient, good quality sleep is essential for maintaining neuro-cognitive health. Sleep-disordered breathing including obstructive sleep apnea (OSA) can lead to reduced intracranial oxygen supply, fragmented sleep, and other negative effects that have been linked to cognitive impairment [1]. A growing body of evidence suggests an association between OSA and cognitive impairment including dementia. Repeated episodes of hypoxia/hypercarbia in OSA may cause deficits in attention, memory, executive function, psychomotor function, and language abilities [2–5]. On the other hand, sleep deprivation due to repeated arousals in OSA have a direct impact on cognition, by causing deficits in attention and memory [3,6]. Furthermore, OSA has also been linked to visuospatial deficits [7]. Therefore, untreated OSA may impair cognitive

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<https://doi.org/10.1016/j.sleep.2023.11.017>

Received 22 July 2023; Received in revised form 31 October 2023; Accepted 8 November 2023

Available online 11 November 2023

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health and contribute to the development of neurodegenerative diseases [7].

Elucidating the mechanisms associating OSA with cognitive impairment is important for optimizing the strategies on dementia prevention. Events of sleep apnea result in repeated episodes of hypoxia, leading to increased oxidative stress and inflammation [8]. Arousals and interrelated surges of sympathetic nervous system activity due to apnea events may lower the efficacy of the glymphatic system to remove potential neurotoxins accumulating during wakefulness, such as amyloid-beta and protein tau [9]. Noteworthy, stages of sleep may play an important role in nocturnal disordered breathing. Rapid eye movement (REM) sleep is characterized by increased tendency of upper airway collapse due to reduced genioglossus activity [10]. Among individuals with OSA, apnea and hypopnea events during REM sleep are typically longer, more frequent, and are associated with greater oxygen desaturation than events during non-REM sleep [11]. We have previously reported that severe REM-OSA was associated with both carotid intima thickness and protein biomarkers while such a relationship could not be identified for non-REM-OSA [12,13]. Since decreased REM sleep duration also impairs cognitive performance [14,15], apnea and hypopnea events during this sleep stage may be of particular concern for increasing the odds of daytime cognitive dysfunction. Nevertheless, despite the evidence supporting the potential impact of OSA on cognitive health, such as executive function and memory [16], cognitive studies focusing on OSA during REM sleep are scarce. Due to its versatility, reliability, and sensitivity to cognitive impairment, Trail Making Test (TMT) is widely accepted as part of assessments to provide a comprehensive evaluation of cognitive function [17]. Therefore, we examined the association between the performance on the TMT and apnea-hypopnea index (AHI) in the total sleep period and in REM sleep. We hypothesized that worse performance on the TMT would be associated with both higher AHI and higher AHI during REM sleep.

### 3. Methods

#### 3.1. Study population

This was a community-based, cross-sectional study among Swedish adults. The study population comprised women from the follow-up of the cohort study "Sleep and Health in Women" (SHE), and men from the study "Men in Uppsala; a Study of sleep, Apnea and Cardiometabolic Health" (MUSTACHE). The SHE study started in year 2000, when a sleep/health questionnaire was sent to a random sample of women aged >20 years from the population registry of the City of Uppsala, Sweden (response rate of 71.6 %). Of the responders aged 20–70 years ( $n = 6112$ ), a random sample of 400 women, with an oversampling of snorers, participated in Phase II of the study and was investigated with a whole night polysomnography (PSG), questionnaires, anthropometric measurements and blood sampling during 2001–2004 [18]. In a follow-up during 2012–2014, 273 of the original participants performed a new PSG together with 127 randomly selected women in the same age range from the original cohort, yielding a total of 400 women who were included in the present study. The MUSTACHE study was initiated in 2016 when men participating in the community-based study EpiHealth during 2011–2015 ( $n = 9377$ ) [19], matched with the women in the SHE cohort by age and BMI, were recruited. As all participants in EpiHealth were older than 45 years at the time for inclusion in the present study, for the youngest age group a matching man was instead recruited from the community by local announcements ( $n = 59$ ). The men were investigated with a whole night PSG, questionnaires, anthropometric measurements and blood sampling using the same protocol as for the SHE-study [13].

The recruitment flowchart is shown in Fig. 1. Among the initially eligible participants (400 women, 400 men), 12 had incomplete or missing information in PSG or cognitive test results. Another 59 participants had missing information in one or more of the potential confounding factors. One participant was defined as an outlier in the cognitive performance test (more than 4 SD apart from the mean value

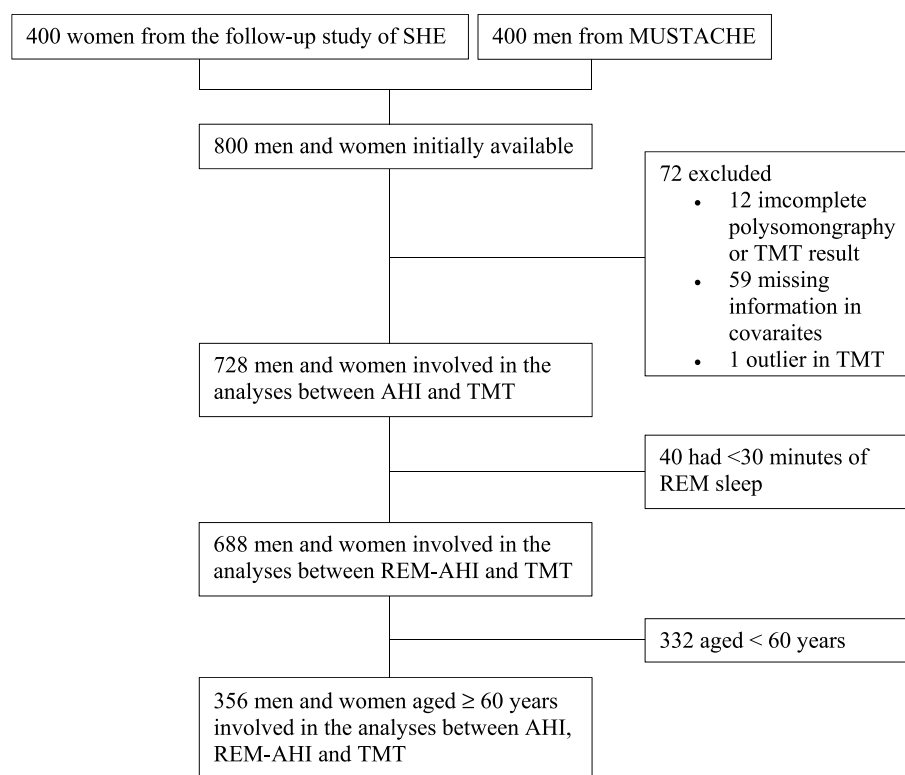


Fig. 1. Inclusion criteria of the study population.

of the test score) and was excluded. Therefore, 728 participants were involved in the study. We further excluded participants with less than 30 min of REM sleep recorded by PSG ( $n = 40$ ) for the analyses in which AHI during REM sleep was the independent variable. Written informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee at Uppsala University, Uppsala, Sweden (approval number 2009/379 and 2016/029).

### 3.2. Assessment of sleep by polysomnography

All participants underwent a whole-night ambulatory PSG using the same equipment (EMBLA, Flaga Inc., Iceland). Home-based use of the device has been proven to generate comparable sleep parameters with in-laboratory PSG test [20]. Sleep was scored manually by the same investigator following the Sleep Scoring Manual of the American Academy of Sleep Medicine (version 2) [21]. AHI was calculated as the number of apnea and hypopnea events divided by the total duration of sleep (in hours). REM-AHI was calculated as the number of apnea and hypopnea events occurring during REM sleep stage divided by the total duration of REM sleep (in hours). Oxygen desaturation index (ODI) was calculated as the number of times that the oxygen saturation level drops by 3 % or more during sleep divided by the total sleep duration (in hours). AHI and REM-AHI were categorized into the following four levels of OSA: normal/no (<5 events/h), mild (5 to <15 events/h), moderate (15 to <30 events/h), and severe ( $\geq 30$  events/h) OSA.

### 3.3. Cognitive function

Participants' cognitive function was assessed by TMT during the day after the overnight PSG measurement at the test center at 8–10 a.m. TMT is a neuropsychological test that assesses a person's cognitive processing speed and conflict monitoring skills as a measure of executive functions [22]. It consists of two parts, part A and B. Part A involves connecting a series of numbered circles in ascending order. Part B involves connecting a series of circles that alternate between numbers and letters in alphabetical and numerical order (e.g., 1-A-2-B-3-C, etc.). Prior to commencing the TMT, participants were explained how to perform the task, including brief trial runs, to guarantee their comprehension of the procedure. Participants were instructed to complete these subtests as quickly as possible. The total time needed (in seconds) to correctly connect all symbols during each subtest, which included the time to correct erroneously chosen paths was recorded. A shorter time taken to completing each part indicates better cognitive performance.

#### 3.3.1. Assessment of covariates

Selection of potential confounding factors was based on subject matter knowledge guided by directed acyclic graphs. These factors included age, sex, level of education, leisure-time physical activity, smoking status, alcohol consumption, body mass index (BMI), systolic blood pressure, diabetes, and history of stroke. Age, sex, and history of diseases were recoded when participants visited the test center. Level of education, leisure-time physical activity, smoking status, and alcohol consumption were assessed by questionnaires. Leisure-time physical activity was asked as "How frequently do you exercise or physically strain yourself during free time?" with corresponding options of "Sedentary: spend most of the leisure-time sitting"; "Light: walk, ride a bike or do similar light activities a couple of hours per week"; "Moderate to intense: exercise (e.g. jogging, swimming) regularly or even engage in intense exercise training". Blood pressure and anthropometry data was measured at the test center. BMI was calculated as weight in kilogram divided by the square of height in meter.

### 3.4. Statistical analysis

Associations between parameters of sleep apnea and outcomes of TMT were analysed using linear regression. AHI or REM-AHI was chosen

as the independent variable in the analyses on the full study population or subsamples. The associations between levels of AHI or REM-AHI (as mentioned above) with TMT were also determined, in which the lowest level (<5 events/h) was set as the reference. The associations were analysed first in an age-adjusted model, then in a model adjusting for age, sex, education, leisure time physical activity, smoking status, and alcohol consumption (Model 1), and finally in a model additionally adjusting for BMI, systolic blood pressure, diabetes, and history of stroke (Model 2). Distribution of the residuals in the linear regression was examined by Q-Q plot. As cognitive impairment occurs primarily in older adults, analyses focusing on a subsample of participants aged  $\geq 60$  years and with  $\geq 30$  min of REM sleep were performed. Statistical analyses were conducted using Stata 17.1 (Stata Corporation, College Station, TX, USA). A two-tailed  $P$  value of less than 0.05 was regarded statistically significant.

#### 3.4.1. Secondary analyses

A set of sensitivity analyses were performed in the full study population. Associations between ODI and TMT results, as well as the associations between percentage of total sleep time with oxygen saturation below 90 % and TMT results were examined. In addition, the ratio between TMT-B and TMT-A was calculated as an additional measurement of executive functions [23], and its potential correlations with AHI and REM-AHI were tested. We also performed analyses for testing the potential associations between AHI and REM-AHI with TMT results separated by sex [24].

## 4. Results

Table 1 shows the characteristics of the study population. Participants had a mean age of  $59.1 \pm 11.3$  years. Among the participants, 52 % were women, 29 % had moderate or severe OSA (AHI  $\geq 15$ ) according to the overnight PSG record. Among those who had at least 30 min of REM sleep during the PSG measurement, 44 % had a REM-AHI of  $\geq 15$  events/hour. TMT-A and TMT-B results differed between AHI and REM-AHI groups when the cut-off was set at 15 events/hour. Details of the PSG report on sleep and sleep breathing parameters are given in **Supplement (Table S1)**.

The association between AHI during the whole night and TMT-derived cognitive function is exhibited in Table 2. There was no association between AHI and TMT-A or TMT-B results. When participants without sleep apnea (AHI <5) were set as the reference group, difference in TMT-A results was not detected between them and participants with mild, moderate, or severe sleep apnea. Compared to participants without sleep apnea, those with mild sleep apnea showed a decreased time for completing TMT-B ( $\beta$ -coefficient: 5.93, 95 % CI: [-11.08, -0.77],  $P = 0.024$ , Model 2). The difference remained significant after we merged the three groups with sleep apnea (AHI  $\geq 5$  vs AHI <5,  $\beta$ -coefficient: 4.83, 95 % CI: [-9.44, -0.22],  $P = 0.040$ , Model 2). However, no difference in TMT-B was found when AHI = 15 was used as the cut-off point (AHI  $\geq 15$  vs AHI <15,  $\beta$ -coefficient: 0.33, 95 % CI: [-5.08, 4.42],  $P = 0.891$ , Model 2).

Analysis results for the possible link between OSA during REM sleep and TMT are given in Table 3. We did not find any association between REM-AHI or REM-AHI categories and TMT results in all participants with  $\geq 30$  min of REM sleep. However, when focusing on the participants aged  $\geq 60$  years, we found that compared to those with lower REM-AHI, a REM-AHI between 5 and 14.9 was associated with longer time finishing the TMT-A ( $\beta$ -coefficient: 5.16, 95 % CI: [1.41, 8.90],  $P = 0.007$ , Model 2). Similar trend was observed between participants with a REM-AHI <5 and groups with REM-AHI between 15 and 29.9 or  $\geq 30$  (Fig. 2). We further merged the three categories with REM-AHI  $\geq 5$  and compared the new category with REM-AHI <5, the difference in TMT-A result remained (REM-AHI  $\geq 5$  vs REM-AHI <5,  $\beta$ -coefficient: 3.93, 95 % CI [0.96, 6.90],  $P = 0.010$ , Model 2).

Sensitivity analyses using ODI as the main exposure variable did not

**Table 1**  
Characteristics of the participants.

Characteristics	All	Severity of sleep apnea					
		AHI<15	AHI≥15	P	REM-AHI<15*	REM-AHI≥15*	P
Number of participants	728	517	211		386	302	
Age, yrs	59.1 ± 11.3	56.6 ± 11.3	65.2 ± 8.7	<0.001	54.8 ± 11.7	63.5 ± 8.8	<0.001
Sex, n (%)				0.04			<0.001
Women	375 (51.5)	254 (49.1)	121 (57.4)		165 (42.7)	187 (61.9)	
Men	353 (48.5)	263 (50.9)	90 (42.7)		221 (57.3)	115 (38.1)	
Education, n (%)				0.02			<0.001
Elementary	204 (28.0)	136 (26.3)	68 (32.2)		93 (24.1)	96 (31.8)	
Secondary	233 (32.0)	157 (30.3)	76 (36.0)		109 (28.2)	111 (36.8)	
College/University	291 (40.0)	224 (43.3)	67 (31.8)		184 (47.7)	95 (31.5)	
Systolic Blood Pressure, mmHg	131.5 ± 16.3	129.6 ± 16.0	136.1 ± 16.4	<0.001	128.2 ± 15.4	134.9 ± 16.2	0.004
Body mass index, kg/m <sup>2</sup>	26.4 ± 4.5	25.7 ± 4.2	28.3 ± 4.9	<0.001	25.0 ± 3.9	27.8 ± 4.5	<0.001
Stroke, n (%)	20 (2.8)	11 (2.1)	9 (4.3)	0.11	6 (1.6)	13 (4.3)	0.03
Diabetes, n (%)	33 (4.5)	19 (3.7)	14 (6.6)	0.08	14 (3.6)	18 (6.0)	0.15
Leisure time physical activity, n (%)				<0.001			<0.001
Sedentary	56 (7.7)	35 (6.8)	21 (10.0)		25 (6.5)	27 (8.9)	
Light	451 (62.0)	299 (57.8)	152 (72.0)		214 (55.4)	207 (68.5)	
Moderate to intense	221 (30.3)	183 (35.4)	38 (18.0)		147 (38.1)	68 (22.5)	
Smoking status, n (%)				0.15			<0.001
Never	409 (56.2)	301 (58.2)	108 (51.2)		245 (63.5)	144 (47.7)	
Former	271 (37.2)	181 (35.0)	90 (42.7)		114 (29.5)	137 (45.4)	
Current	48 (6.6)	35 (6.8)	13 (5.2)		27 (7.0)	21 (7.0)	
Alcohol consumption, n (%)				0.13			0.08
None	62 (8.5)	43 (8.3)	19 (9.0)		34 (8.8)	22 (7.3)	
Less than 4 drinks per month	397 (54.5)	296 (57.3)	101 (47.9)		225 (58.3)	157 (52.0)	
More than 4 drinks per month	152 (20.9)	101 (19.5)	51 (24.2)		79 (20.5)	65 (21.5)	
More than 4 drinks per week	117 (16.1)	77 (14.9)	40 (19.0)		48 (12.4)	58 (19.2)	
Trail making test A result, s	34.4 ± 11.8	33.2 ± 11.6	37.2 ± 11.9	<0.001	32.2 ± 11.3	36.4 ± 11.5	<0.001
Trail making test B result, s	75.2 ± 30.3	72.1 ± 28.8	83.0 ± 32.3	<0.001	70.0 ± 27.8	79.3 ± 29.7	<0.001
Trail making test B/A ratio	2.24 ± 0.69	2.23 ± 0.69	2.28 ± 0.69	0.37	2.23 ± 0.69	2.23 ± 0.63	0.95

Data presented as mean ± standard deviation or n (%) in column). \* Participants with ≥30 min of REM sleep recorded by overnight polysomnography (n = 688). P values refer to one-way analysis of variance or Pearson's chi-squared test.

**Table 2**  
Association between apnea-hypopnea index (AHI) and Trail Making Test (TMT) results.

Association with TMT-A result in seconds	n	Age adjusted			Model 1			Model 2		
		β-coefficient	(95 % CI)	P	β-coefficient	(95 % CI)	P	β-coefficient	(95 % CI)	P
AHI, events/hr	728	−0.005	(−0.06, 0.05)	0.859	−0.01	(−0.06, 0.04)	0.644	−0.002	(−0.05, 0.06)	0.954
AHI categories										
0–4.9	316	reference	reference		reference	reference		reference	reference	
5–14.9	201	−0.15	(−2.11, 1.81)	0.881	−0.08	(−2.06, 1.90)	0.937	0.18	(−1.83, 2.19)	0.858
15–29.9	128	0.09	(−2.23, 2.40)	0.941	−0.28	(−2.62, 2.05)	0.812	0.08	(−2.31, 2.46)	0.949
≥30	83	−0.42	(−3.15, 2.32)	0.764	−0.54	(−3.30, 2.21)	0.699	0.04	(−2.82, 2.90)	0.977
Association with TMT-B result in seconds										
AHI, events/hr	728	−0.02	(−0.16, 0.11)	0.721	−0.05	(−0.18, 0.09)	0.490	−0.07	(−0.21, 0.07)	0.341
AHI categories										
0–4.9	316	reference	reference		reference	reference		reference	reference	
5–14.9	201	−5.14	(−10.19, −0.10)	0.046	−5.49	(−10.56, −0.43)	0.033	−5.93	(−11.08, −0.77)	0.024
15–29.9	128	−0.19	(−6.15, 5.77)	0.949	−1.73	(−7.72, 4.26)	0.570	−2.31	(−8.42, 3.80)	0.459
≥30	83	−4.31	(−11.35, 2.72)	0.229	−4.57	(−11.63, 2.49)	0.204	−5.65	(−12.98, 1.68)	0.131

Model 1, adjusted for age, sex, education, leisure time physical activity, smoking status, alcohol consumption; Model 2, adjusted for age, sex, education, leisure time physical activity, smoking status, alcohol consumption, BMI, systolic blood pressure, diabetes, and history of stroke.

suggest any association with TMT results (Supplement Table S2). No association between AHI or REM-AHI and TMT-B/A ratio was detected, nor was there any differences between AHI or REM-AHI categories regarding TMT-B/A ratio. Results of the analyses on participants aged <60 years and with with ≥30 min of REM sleep, as well as sex-stratified analyses are given in Supplement Tables S3–S5.

## 5. Discussion

The present study aimed to investigate the relationship between OSA and cognitive function, specifically focusing on the impact of AHI during

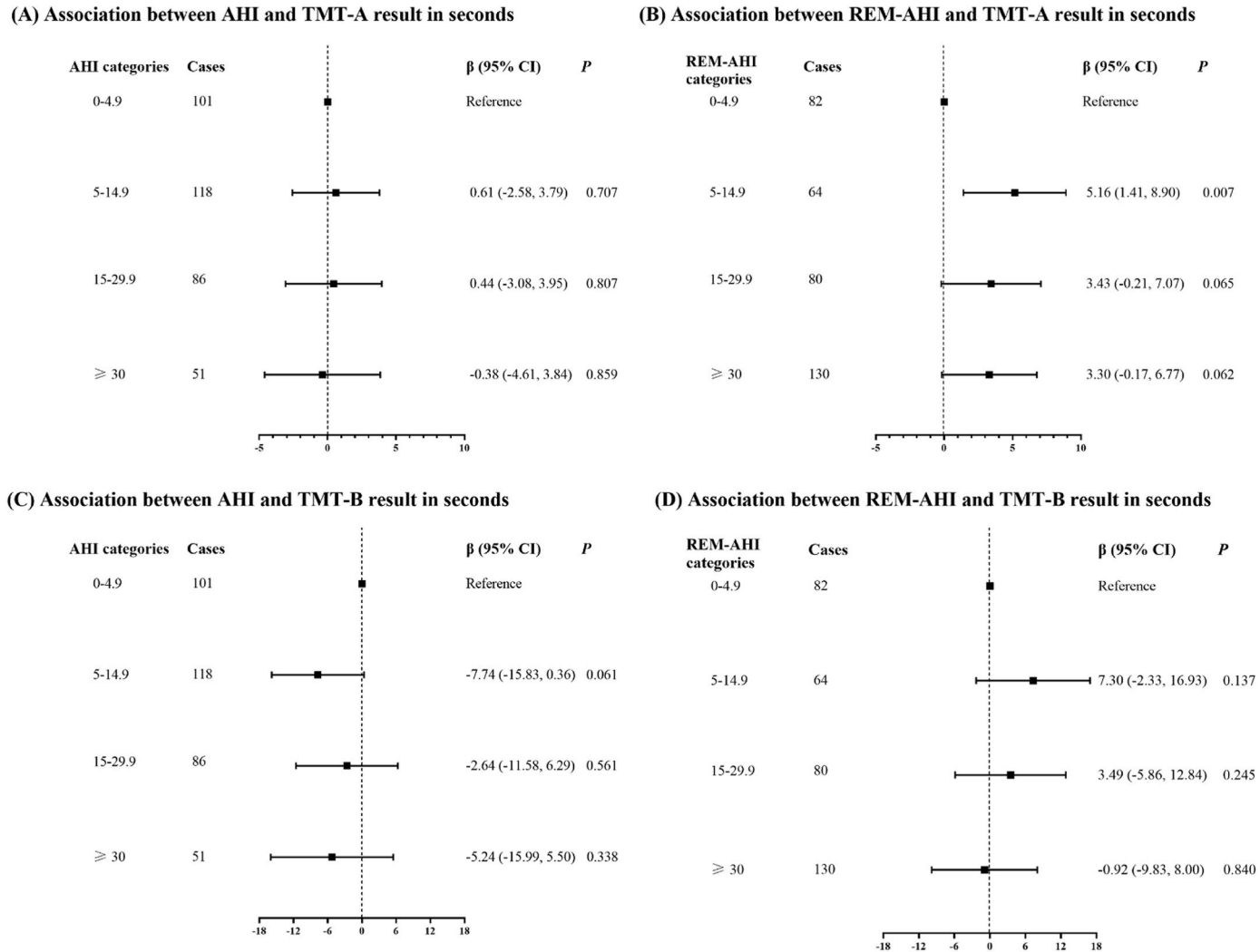
REM sleep. The full study population was relatively young and when focusing on individuals aged 60 and above, AHI during REM sleep was associated with worse executive function and attention assessed by TMT-A. Interestingly, this association was not observed with total AHI, suggesting a possibly unique role of REM sleep in the effect of OSA on cognition. These findings support the hypothesis that events of sleep apnea during REM sleep may have a greater impact on cognitive function.

The detrimental effects of OSA on cognitive function have been attributed to several factors, including reduced intracranial oxygen supply, fragmented sleep, and increased oxidative stress and

**Table 3**  
Association between apnea hypopnea index during REM sleep (REM-AHI) and Trail Making Test (TMT) results among participants had  $\geq 30$  min of REM sleep.

Association with TMT-A result in seconds	N	Age adjusted			Model 1			Model 2		
		$\beta$ -coefficient	(95 % CI)	P	$\beta$ -coefficient	(95 % CI)	P	$\beta$ -coefficient	(95 % CI)	P
REM-AHI, events/hr	688	0.01	(-0.04, 0.05)	0.754	-0.01	(-0.05, 0.04)	0.821	0.01	(-0.04, 0.06)	0.741
REM-AHI categories										
0–4.9	253	reference	reference		reference	reference		reference	reference	
5–14.9	133	0.85	(-1.37, 3.07)	0.451	0.82	(-1.41, 3.05)	0.471	1.04	(-1.20, 3.29)	0.362
15–29.9	117	-0.04	(-2.42, 2.33)	0.972	-0.04	(-2.45, 2.37)	0.974	0.36	(-2.11, 2.82)	0.777
$\geq 30$	185	0.99	(-1.16, 3.13)	0.366	0.56	(-1.65, 2.78)	0.618	1.15	(-1.15, 3.46)	0.327
Association with TMT-B result in seconds										
REM-AHI, events/hr	n	$\beta$ -coefficient	(95 % CI)	P	$\beta$ -coefficient	(95 % CI)	P	$\beta$ -coefficient	(95 % CI)	P
REM-AHI categories										
0–4.9	253	reference	reference		reference	reference		reference	reference	
5–14.9	133	0.61	(-4.95, 6.16)	0.830	0.11	(-5.46, 5.67)	0.970	0.20	(-5.41, 5.81)	0.945
15–29.9	117	0.12	(-5.83, 6.08)	0.968	-0.86	(-6.87, 5.15)	0.779	-0.77	(-6.94, 5.40)	0.806
$\geq 30$	185	-1.22	(-6.59, 4.15)	0.656	-3.44	(-8.98, 2.09)	0.222	-3.22	(-8.99, 2.54)	0.272

Model 1, adjusted for age, gender, education, leisure time physical activity, smoking status, alcohol consumption; Model 2, adjusted for age, sex, education, leisure time physical activity, smoking status, alcohol consumption, BMI, systolic blood pressure, diabetes, and history of stroke.



**Fig. 2.** Association between sleep apnea and Trail Making Test (TMT) results among participants aged  $\geq 60$  years and had  $\geq 30$  min of REM sleep ( $n = 356$ ) Linear association analysis adjusted for age gender, education, leisure time physical activity, smoking status, alcohol consumption, BMI, systolic blood pressure, diabetes, and history of stroke.



inflammation [25,26]. In addition, a study has demonstrated that apnea-induced sleep deprivation can lead to deficits in attention and memory [27]. The present study adds to this body of literature by highlighting the importance of the timing of obstructive events during sleep in relation to cognitive function. In addition, our finding suggests that OSA during REM sleep may be of particular concern for its potential detrimental impact on cognitive function. In line with our finding, previous research suggests that intermittent hypoxia and sleep fragmentation occurring due to OSA during REM sleep is linked with pathophysiological changes related to cognitive function. One study tested 96 men and women (aged  $65.2 \pm 6.4$  years) with AHI ranged between 0 and 97, and found that more respiratory events during REM sleep were associated with reduced daytime regional cerebral blood flow in the bilateral ventromedial prefrontal cortex and in the right insula extending to the frontal cortex [28]. Another study suggests that alterations of REM sleep spectral power values are associated with neurodegeneration and neocortical amyloid deposition in older adults [29].

The mechanism underlying the impact of obstructive events during REM sleep on cognitive function is not fully understood. One possible explanation is that REM sleep is a critical stage for memory consolidation and cognitive function. Decreased REM sleep duration has been associated with impaired cognitive performance [30,31]. Therefore, OSA during REM sleep may disrupt the normal functioning of this critical stage, leading to cognitive deficits. Another possible explanation is that the tendency for upper airway collapse is increased during REM sleep, leading to longer and more frequent apnea and hypopnea events during this stage [32]. These events may result in greater oxygen desaturation, which has been linked to cognitive impairment. Observation from the present study does not show a clear association between severity of OSA during REM sleep and cognitive performance, whether a linear association exists between REM-AHI and TMT results remains to be further investigated utilizing larger study sample.

Noteworthy, the impact of OSA during REM sleep on cognitive performance was only reflected by TMT-A in our study. Similarly, a cross-sectional study of 755 community-dwelling adults (aged  $62.3 \pm 8.2$  yrs) from the Wisconsin Sleep Cohort found no association between REM-AHI and cognitive measurement results including TMT-B [33]. Some reasons might explain why TMT-A showed a significant difference between the older adults with and without OSA in our study, while TMT-B did not. One possibility is that TMT-A and TMT-B assess different cognitive functions. TMT-A primarily measures processing speed and attention, while TMT-B measures more complicated executive functions such as set shifting and working memory [22]. Therefore, it is possible that processing speed and attention is more sensitive than complex executive function following a night's sleep with REM-related apnea. On the other hand, compared to TMT-B, TMT-A was easier to learn and less prone to practice effects, resulting in a clearer distinction between the two groups. In addition, in both the Wisconsin Sleep Cohort and the present study, the participants were relatively young, with a generally good cognitive health status, thus conventional tools for assessing cognitive decline are not sensitive enough to detect the impact of OSA on cognition. It must also be kept in mind that the cognitive assessments in the present study were conducted following a single night PSG measurement, thus the association between TMT-B result and apnea during REM sleep cannot be ruled out if REM-AHI was determined based on multi-night PSG measurement.

We also found in the full sample of the study that those with mild OSA finished TMT-B quicker than participants without OSA, indicating a better executive function. There was also a trend in the subgroup of >60 years old in that regard. These results are counterintuitive to the general hypothesis that even mild OSA may impair cognitive performance. However, preliminary findings from animal studies suggest a neuroprotective role of intermittent hypoxia through a preconditioning-like effect [34]. Whether such a mediating effect for the neurons exist behind mild OSA induced hypoxia and executive function in humans remain to be investigated.

Several limitations should be acknowledged in the present study. First, the study design was cross-sectional, which limits the ability to establish causality. Longitudinal studies are needed to determine the temporal relationship between OSA and cognitive function. Second, the association between OSA during REM Sleep and cognition was observed among a subsample of the study, which restricted the statistical power of our analyses. Third, although the study controlled for potential confounding factors, it is possible that other unmeasured factors may have influenced the results, and the first night effect of PSG may reduce the representativeness for normal sleep patterns of the participants. Finally, the study did not investigate the impact of treatment for OSA on cognitive function. It is possible that treatment may improve cognitive function in individuals with OSA [35], and future studies should explore this possibility. Despite these limitations, the present study has important implications for clinical practice and future research. The results suggest that assessing AHI during REM sleep may be a more sensitive marker of cognitive impairment compared to total AHI. Therefore, clinicians may consider assessing AHI during REM sleep when evaluating cognitive function in individuals with OSA. Future research should further investigate the mechanism underlying the impact of apnea events during REM sleep on cognitive function, as well as the potential benefits of treatment for OSA on cognitive function.

In conclusion, the present study provides preliminary evidence of an association between AHI during REM sleep and cognitive function among older adults, particularly in attention-related tasks. These findings suggest that apnea events during REM sleep may have an impact on cognitive function. The present study highlights the importance of considering the timing of apnea events during sleep when evaluating its potential impact on cognitive health.

#### Financial disclosure

This research was supported by the Swedish Heart Lung Foundation (EL, 20220416).

#### Non-financial disclosure

none.

#### CRediT authorship contribution statement

**Xiao Tan:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Mirjam Ljunggren:** Methodology, Investigation, Data curation, Writing – review & editing. **Lena Kilander:** Investigation, Writing – review & editing. **Christian Benedict:** Investigation, Writing – review & editing. **Eva Lindberg:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgements

EL and XT conceptualized the study. EL and ML contributed to data acquisition. XT and EL performed statistical analysis, interpreted the data, and wrote the original draft. All authors contributed with critical reading and edited the draft, reviewed and approved the final version of the article prior to submission. EL and XT are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This research was supported by the Swedish Heart Lung

Foundation (EL, 20220416). The funders had no role in the design and conduct of the study, nor the decision to prepare and submit the manuscript for publication.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2023.11.017>.

## Abbreviation List

AHI	apnea-hypopnea index
BMI	body mass index
MUSTACHE	Men in Uppsala; a Study of sleep, Apnea and Cardiometabolic Health
OSA	obstructive sleep apnea
PSG	polysomnography
REM sleep	rapid eye movement sleep
REM-AHI	apnea-hypopnea index during rapid eye movement sleep
SHE	Sleep and Health in Women Study
TMT	trail making test

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