

Interaction of obstructive sleep apnoea and cognitive impairment with slow gait speed in middle-aged and older adults

SUNGHEE LEE¹, CHOL SHIN^{1,2}

¹Institute of Human Genomic Study, School of Medicine, Korea University Ansan Hospital, Ansan, The Republic of Korea

²Division of Pulmonary, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, The Republic of Korea

Address correspondence to: C. Shin, Institute of Human Genomic Study, School of Medicine, Korea University Ansan Hospital, 516 Gojan-1-dong, Danwon-gu, Ansan-si, Gyeonggi-do 15355, The Republic of Korea. Tel: (+82) 31 412 5603; Fax: (+82) 31 412 5604. Email: chol-shin@korea.ac.kr

Abstract

Objective: to investigate whether slow gait speed is associated with cognitive impairment and further whether the association is modified by obstructive sleep apnoea (OSA).

Methods: in total, 2,222 adults aged 49–80 years, free from dementia, stroke and head injury were asked to walk a 4-m course at fast and usual gait speeds. The time taken to walk was measured. All participants completed the Korean Mini-Mental State Examination, which was validated in the Korean language, to assess cognitive function. Additionally, the participants completed a polysomnography test to ascertain OSA (defined as an apnoea–hypopnoea index ≥ 15). Multivariable linear regression models were utilised to test the associations.

Results: time taken to walk 4 m showed significant inverse associations with cognitive scores (P value = 0.001 at fast gait speed and P = 0.002 at usual gait speed). Furthermore, a significant interaction according to OSA on the association between time to walk and cognitive impairment was found (P value for interaction = 0.003 at fast gait speed and P value for interaction = 0.007 at usual gait speed).

Conclusion: we found that the inverse association between the time taken to walk 4 m and a cognitive score became significantly stronger, if an individual had OSA.

Keywords: *gait, cognition, obstructive sleep apnoea, older people*

Introduction

Gait speed, measured with the time taken to walk 4 m at fast and usual gait speeds, is an important geriatric measurement that indicates age-related decline in physical and cognitive function [1–4] among older adults. Previous epidemiological studies demonstrated that gait speed was an independent predictor for cognitive impairment [1–4]. Specifically, the temporal sequence between slower gait speed and cognitive decline has been confirmed [1, 3–6].

Obstructive sleep apnoea (OSA) among older adults and the slower gait speed share a common attribute of muscle ageing. Characterised as nocturnal intermittent hypoxia during sleep [7], OSA in older adults is primarily attributable to airway collapse due to muscle ageing [8], whereas OSA in younger adults is mostly due to a sensitive ventilator control

[8]. Epidemiological studies showed that OSA is more prevalent in older adults than in younger adults [9]. OSA has been indicated to have strong associations with brain structural changes such as cerebral white matter change (WMC) [10] and functional changes such as cognitive impairment [7, 11]. We previously reported that middle-aged and older adults with OSA were likely to have a 2-fold increased risk of WMC compared with those without OSA [10].

However, no study has yet investigated the modifying effect of OSA status on the association between gait speed and cognitive impairment in a large general population. Therefore, we aimed to examine the interaction according to OSA on the association between slower gait speed and cognitive impairment among 2,222 well-functioning community-dwelling adults. We hypothesised that individuals with OSA would be at substantially higher risk of cognitive impairment associated with slow gait speed than those

without OSA. To test this hypothesis, we utilised the Korean Genome and Epidemiology Study (KoGES) data.

Methods

Study population

The KoGES cohort, an ongoing prospective cohort study, was initiated in 2001 to evaluate the risk and the burden of chronic diseases among the general population. Detailed information on the KoGES cohort has been previously published [12]. Briefly, at baseline enrolment from 2001 to 2002, the initial cohort of 5,020 adults aged 40–69 years in Ansan, South Korea was randomly recruited by telephone contact with 10,957 individuals [12]. Because the penetration of telephone lines in Ansan was very high, recruitment using a telephone directory allows for random selection to enrol a representative sample from the general population [12]. According to demographic characteristics such as age and gender of the 2000 census, the cohort was recruited with a two-stage cluster sampling, comprising 2,523 men (50.26%) and 2,497 women (49.74%). Since then, the study participants have been biennially followed up. During their visits, the participants underwent comprehensive tests including a physical examination, an interviewer-administrated questionnaire, and biochemical and clinical examinations. Research staff members were professionally trained on standardised protocols. The study participants, wearing light clothing without shoes, were measured for height and weight. Venipuncture was performed on all participants early in the morning at each visit after at least 8 h of fasting. The blood samples were sent to the Seoul Clinical Laboratory (Seoul, South Korea). All participants signed an informed consent form. The current study abided by the ethical rules for human research stated in the Declaration of Helsinki. The Human Subjects Review Committee and the Institutional Review Board of our research centre approved this study.

As a sub-study for ageing, geriatric measurements including a cognitive test, sleep polysomnography and a motor test were initiated and followed up every 4 years starting from the 6th follow-up visit (16 February 2011 to 27 December 2014). Of 3,052 participants who visited at the 6th follow-up, we excluded 466 participants due to incomplete data on cognitive test, gait test or sleep polysomnography. Of 2,586 participants who completed all three tests, we further excluded 60 participants who had been diagnosed with dementia ($n = 5$) or stroke ($n = 55$). Additionally, 304 participants were excluded due to missing covariates (291 smoking, 11 diabetes and 2 educational information). Thus, a total of 2,222 participants (942 men and 1,280 women) aged 50–80 years were in the final analyses.

Gait speed

Measurement of the time taken to walk a 4-m course was utilised to ascertain gait speed. All participants were asked to walk a 4-m course along the hallway at fast (maximum

and usual gait speeds. Using a stopwatch, a research staff member recorded the time taken by each participant to walk from the starting point to the end point of the 4-m course. We calculated the speed (m/s) by dividing the 4-m distance by the time taken to walk in seconds. For example, if a participant walked at slow speed across 4 m, then the participant would have a lower gait speed and a longer time to walk 4 m. The measurement of gait speed was introduced by the National Institute of Health (NIH) as a comprehensive geriatric assessment tool [13]. The reliability of the gait speed has been validated [14].

Polysomnography

An overnight polysomnography test was assessed with the Embla portable sleep monitoring system (Embletta[®] X100, Embla, USA). Apnoeas and hypopnoeas were ascertained according to the guideline from the American Academy of Sleep Medicine [15]. The apnoea–hypopnoea index (AHI) was determined by averaging the number of events per hour. OSA was defined as having AHI ≥ 15 . These polysomnography data were scored by two professionally trained technicians with more than 5 years of experience. Both the intra-rater reliability for two raters (Cronbach's $\alpha = 0.996$ and 1.00) and the inter-rater reliability for AHI were high (Cronbach's $\alpha = 0.998$).

Cognitive measurement

The Mini-Mental State Examination (MMSE), the most widely used global cognitive screening test [16], has been used not only in clinical evaluations but also in research for the diagnosis of mild cognitive impairment or dementia, particularly to screen individuals at the high risk of cognitive impairment. The K-MMSE, validated in the Korean language [17], has a maximum possible score of 30.

Statistical analysis

T-test, analysis of variance and chi-square test were utilised to examine the continuous and categorical variables of descriptive characteristics. Kruskal–Wallis tests were used to compare categorical variables. The significance of trend according to the tertile categories of gait speed was examined. To assess the associations, multivariable linear regression models were established after adjusting for the following potential confounding variables: age, sex, body mass index (BMI), education, current smoker, current drinker, physical activity, hypertension, diabetes, total cholesterol, high-sensitivity C-reactive protein (hs-CRP) and depression (Beck's Depression Index, BDI). To control for potential influence from height on gait speed, we additionally adjusted for height. A two-sided *P* value of <0.05 was considered significant. SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was performed for all the statistical analyses.

Results

General characteristics according to the tertile range of the time taken to walk 4 m

Table 1 presents the general characteristics based on the tertile range of the time taken to walk 4 m at a usual gait speed among 2,222 participants (942 men and 1,280 women). As the time taken to walk 4 m (s) increased, the gait speed (m/s) decreased. According to the tertile range, the average age of the participants showed an increasing trend (P value for trend <0.001). A slower gait speed was associated more with women than with men ($P < 0.001$). Those with slower gait speed were more likely to have higher BMI ($P = 0.016$), higher systolic blood pressure ($P < 0.001$), higher frequency of hypertension ($P < 0.001$) and diabetes ($P < 0.001$). Unexpectedly, a slower gait speed was associated with individuals who drank less ($P < 0.001$) and smoked less ($P = 0.001$). This might indicate behavioural changes followed by changes in health status including muscle ageing. Those with a slower gait speed had a higher level of hs-CRP ($P = 0.037$), higher depression index ($P < 0.001$) and a lower K-MMSE score ($P < 0.001$).

General characteristics of the study participants according to OSA

Table 2 lists the descriptive characteristics of the 2,222 study participants according to OSA status. Compared with participants without OSA, participants with OSA were more likely to be older ($P < 0.001$) and male ($P < 0.001$).

They also had a higher BMI ($P < 0.001$), higher systolic ($P < 0.001$) and higher diastolic blood pressure ($P < 0.001$). The frequency of current drinkers and current smokers among participants with OSA was higher ($P = 0.005$ and $P < 0.001$, respectively). The participants with OSA had a higher prevalence of hypertension and diabetes (both $P < 0.001$). The level of hs-CRP was higher among the participants with OSA ($P < 0.001$). The individuals with OSA had a lower depression index ($P = 0.027$). Importantly, the cognitive functional score, measured with K-MMSE, was significantly lower in those with OSA than in those without OSA ($P = 0.017$). However, OSA caused no difference in the walking time ($P = 0.082$ at fast gait speed and $P = 0.082$ at usual gait speed).

Significantly modifying effect according to OSA on the association between the time taken to walk 4 m and a cognitive impairment

Table 3 presents a significantly modifying effect according to OSA on the associations between the time taken to walk 4 m at fast and usual gait speeds and the cognitive functional score, measured with K-MMSE among 2,222 participants. Particularly, significant inverse associations between the time taken to walk the 4-m course and cognitive impairment were substantially higher among those with OSA, compared with those without OSA ($\beta = -0.70$ versus $\beta = -0.21$, P value for interaction = 0.003 at fast gait speed; $\beta = -0.40$ versus $\beta = -0.13$, P value for interaction = 0.007 at usual gait speed) (Table 3 and Appendix 2, see Supplementary

Table 1. General characteristics according to the tertile range of the time taken to walk 4 m at usual gait speed ($n = 2,222$)

	Gait speed			<i>P</i> value for trend
	T1, <i>n</i> = 744	T2, <i>n</i> = 740	T3, <i>n</i> = 738	
Time to walk 4 m (s)	3.22 ± 0.29	3.93 ± 0.19	4.90 ± 0.67	
Gait speed (m/s)	1.25 ± 0.13	1.02 ± 0.05	0.83 ± 0.09	
Age, year	57.54 ± 5.33	58.81 ± 6.58	62.44 ± 7.83	<0.001
Female, <i>n</i> (%)	48.52	59.86	64.50	<0.001
BMI, kg/m ²	24.43 ± 2.98	24.74 ± 2.92	24.80 ± 3.03	0.016
Education, <i>n</i> (%)				
None	0.54	0.54	2.30	<0.001
Elementary	0.81	0.68	3.39	
Middle school	8.87	12.03	19.11	
High school	61.02	65.00	60.16	
University	28.76	21.76	15.04	
Systolic BP, mmHg	114.02 ± 13.65	115.04 ± 14.29	118.29 ± 31.75	<0.001
Diastolic BP, mmHg	75.50 ± 9.37	74.69 ± 9.27	75.05 ± 31.38	0.658
Total cholesterol, mg/dl	194.54 ± 33.41	195.99 ± 35.21	191.36 ± 37.14	0.084
Hypertension, <i>n</i> (%)	30.65	35.95	44.85	<0.001
Diabetes, <i>n</i> (%)	15.05	14.59	21.82	<0.001
Current drinking, <i>n</i> (%)	46.37	42.43	34.01	<0.001
Current smoking, <i>n</i> (%)	35.22	28.24	27.51	0.001
hs-CRP, mg/l ^a	0.56 (0.34, 1.06)	0.63 (0.40, 1.18)	0.70 (0.39, 1.47)	0.037
Physical activity, MET ^a	12.00 (0, 33.00)	11.40 (0, 31.55)	10.13 (0, 29.40)	0.573
Depression index, BDI ^a	6.00 (2.00, 10.00)	6.00 (3.00, 11.00)	7.00 (3.00, 13.00)	<0.001
Cognitive test, MMSE	27.72 ± 1.76	27.72 ± 1.79	27.02 ± 2.48	<0.001
Apnoea–hypopnoea index, AHI ^a	4.10 (1.45, 9.85)	4.50 (1.45, 9.75)	5.05 (2.00, 10.10)	0.766

BP, blood pressure; MET, Metabolic Equivalent Task; mean ± SD.

^aMedian (interquartile range).

data, available at *Age and Ageing* online). Even after adjusting for height, the associations between the time taken to walk the 4 m and cognitive impairment remained significant in both total and OSA populations (Appendix 1, see Supplementary data, available at *Age and Ageing* online).

Discussion

In a population-based cross-sectional study among well-functioning community-dwelling adults, we observed that a cognitive functional score had a significantly inverse association with the time taken to walk 4 m at both fast and usual

Table 2. General characteristics of the study participants according to OSA ($n = 2,222$)

	OSA		P value
	No OSA ($0 < \text{AHI} < 15$) $n = 1,900$ (85.51%)	OSA ($\text{AHI} \geq 15$) $n = 322$ (14.49%)	
Age, year	59.18 \pm 6.81	62.00 \pm 7.41	<0.001
Female, n (%)	61.05	37.27	<0.001
BMI, kg/m^2	24.37 \pm 2.84	26.33 \pm 3.22	<0.001
Education, n (%)			
None	0.84	2.80	0.159
Elementary	1.58	1.86	
Middle school	13.11	14.60	
High school	62.42	59.94	
University	22.05	20.81	
Systolic BP, mmHg	115.24 \pm 22.70	118.94 \pm 13.40	<0.001
Diastolic BP, mmHg	74.73 \pm 20.86	77.16 \pm 9.08	<0.001
Total cholesterol, mg/dl	194.63 \pm 34.47	190.04 \pm 39.83	0.052
Hypertension, n (%)	33.84	56.52	<0.001
Diabetes, n (%)	15.37	27.64	<0.001
Current drink, n (%)	39.74	48.14	0.005
Current smoking, n (%)	28.05	43.79	<0.001
hs-CRP, mg/l^a	0.60 (0.36, 1.15)	0.83 (0.46, 1.55)	<0.001
Physical activity, MET ^a	11.40 (0, 31.60)	7.60 (0, 30.00)	0.147
Depression index, BDI ^a	6.00 (3.00, 11.00)	5.00 (2.00, 11.00)	0.027
Cognitive test, MMSE	27.54 \pm 1.95	27.18 \pm 2.59	0.017
Time to walk 4 m (s)			
Fast	2.93 \pm 0.58	2.99 \pm 0.60	0.082
Usual	4.00 \pm 0.81	4.09 \pm 0.84	0.082
Gait speed (m/s)			
Fast	1.42 \pm 0.26	1.39 \pm 0.27	0.097
Usual	1.04 \pm 0.20	1.02 \pm 0.20	0.081

BP, blood pressure; MET, Metabolic Equivalent Task; mean \pm SD.

^aMedian (interquartile range).

gait speeds, after adjusting for age, sex, BMI, education, smoking, drinking, physical activity, hypertension, diabetes, total cholesterol, hs-CRP and depression. Furthermore, we found that this association between the time taken to walk 4 m and cognitive impairment was significantly modified by OSA status. Even after adjusting for potential confounding factors, the significant interaction by OSA remained. To the best of our knowledge, this is the first study to investigate whether or not the association between slower gait speed and cognitive functional impairment would be aggravated if an individual had OSA. Our current findings in a general population may help us better understand the mechanism of cognitive impairment associated with slow gait speed.

Our findings are consistent with previous findings that demonstrate significant associations with both slower pace of gait speed [1, 3–6] and OSA [7, 11] on cognitive impairment. A 6-year longitudinal study among 108 healthy adults aged 65 years or older found that the walking time (30 ft) significantly predicted cognitive impairment, measured by MMSE ($P = 0.009$) [1]. A previous report by the Health, Ageing, and Body Composition Study demonstrated the association between slower gait speed and cognitive functional decline [18].

Only one previous study examined the effect of gait abnormalities among OSA patients before and after 8-week treatments of continuous positive airway pressure (CPAP), which is a primary clinical treatment for OSA patients to alleviate upper airway obstruction [19]. That study found a substantial but non-significant improvement in gait speed [19]. Particularly, previous studies demonstrated that OSA had a strong association with cognitive impairment [11], particularly due to the lesions in a prefrontal subcortical region [20] which is in control of motor coordination function [21]. Furthermore, a recent meta-analysis with 13 clinical trials revealed that OSA patients with CPAP treatment exhibited a significant improvement on cognitive function related to vigilance [22]. Physical activity has been reported to be beneficial in delaying cognitive impairment [23].

The aetiology for cognitive decline linked to slower gait speed has not fully elucidated. However, previous findings suggested that slower gait speed is attributable to lesions in the prefrontal area [20], which is responsible for both cognitive and motor functions [21]. The lesions resulted from age-related changes that cause brain structural

Table 3. Interaction effect according to OSA on the association between gait speed and cognitive functional score

OSA	n	MMSE					
		Time to walk 4 m (s)					
		Fast gait			Usual gait		
		β	P value	CI	β	P value	CI
Total	2,222	-0.27	0.001	-0.45, -0.12	-0.17	0.002	-0.27, -0.06
No OSA ($0 < \text{AHI} < 15$)	1,900	-0.21	0.009	-0.36, -0.05	-0.13	0.022	-0.24, -0.02
OSA ($\text{AHI} \geq 15$)	322	-0.70	0.006	-1.19, -0.20	-0.40	0.024	-0.74, -0.05
P value for interaction			0.003			0.007	

CI, confidence interval; adjusted for age, sex, BMI, education, smoking, drinking, physical activity, hypertension, diabetes, total cholesterol, hs-CRP and depression.

changes such as volumetric atrophy [24] and age-related WMC [25]. These changes subsequently lead to increased inflammation [25]. Moreover, it has been proposed that cognitive decline associated with OSA, characterised by nocturnal intermittent hypoxia [7], may be linked to a lack of oxygen supply, which leads to increased oxidative stress and inflammation [26]. Oxidative stress is regarded as a contributor to skeletal muscle ageing such as muscle atrophy [27]. Furthermore, a recent finding from an animal study with mice showed that the intermittent hypoxia in OSA causes increased inflammatory markers [28], which further affect cognitive impairment. In this regard, neurocognitive deficits due to increased oxidative stress or inflammation may have an impact on cognitive functional impairment [29].

Older individuals commonly experience gait speed decline as their skeletal muscle ages. In addition, these adults are at high risk of OSA. Both slow gait speed and OSA from muscle ageing increase the risk of cognitive functional impairment. Thus, with the overlapped underlying mechanisms on slower gait speed and OSA linked to cognitive impairment, it is important to identify older adults who might be at an early stage of cognitive impairment by assessing gait speed as well as by diagnosing OSA. Our findings in the current study provide a better understanding of the relationship between gait speed and OSA caused by muscle ageing in an older population in order to ultimately mitigate the burden generated from mild cognitive impairment.

The response rate at baseline indicates data quality necessary to ensure a representative sample, so that the study results can extend to the target population of interest. As previously reported [12], the KoGES has two study sites. Ansan, the current study site, is an urbanised area and the 5,020 participants were enrolled through telephone contacts with 10,957 individuals (a response rate of 45.82%). The second site, Ansung, is a rural area and 2,240 men and 2,780 women were enrolled through attempts to contact 7,192 individuals by mails, door-to-door visits and telephone calls (a response rate by 69.80%). The response rate of Ansan was lower than that of Ansung. However, the study participants were randomly selected from the telephone directory for the general population, so the representativeness of the study population should be valid. Furthermore, to retain valid representativeness, the study participants were randomly selected from the sampling based on the sex and gender distribution.

This ageing sub-study initiated from the 6th follow-up visit of a longitudinal cohort study indispensably has individuals lost to follow-up from the initial cohort. By comparing the general characteristics between the initial cohort participants and the individuals who completed the 6th follow-up, we confirmed no significant difference in age, BMI, education, the prevalence of hypertension and physical activity (Appendix 3, see Supplementary data, available at *Age and Ageing* online). Therefore, we were certain that the missing data were MCAR (missing completely at random) and did not utilise imputation data.

This study has several strengths. First, our study is a large population-based study that has a large sample size from the general population. Second, the participants in the current study were well-functioning community-dwelling older adults without stroke, dementia or head injury. This allowed us to investigate the early stages of physical and cognitive functional impairment. However, this study has also limitations taken into account when interpreting our findings. First, we utilised a cross-sectional study design, which may not infer causality. Second, as a limitation of MMSE, ceiling effects might have affected to be lack of sensitivity to discern cognitive deterioration among healthy participants with early-stage cognitive impairment [30]. However, this potential insensitivity of MMSE among healthy ageing participants did not affect the participants with and without slow gait differently. Thus, the results could only have been underestimated; it supports our findings.

In conclusion, in this population-based cross-sectional study of 2,222 participants, we found a significant inverse association between the time taken to walk 4 m and cognitive function, even after adjusting for potential confounding variables. Furthermore, the association between slower walking time and cognitive impairment became substantially stronger, if an individual had OSA.

Key points

- Older adults are known to have higher prevalence of obstructive sleep apnoea (OSA) than younger adults.
 - The diagnosis of OSA among older adults was primarily attributable to airway collapse due to muscle ageing.
 - Slow gait has been known to be associated with cognitive impairment.
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Supplementary data

Supplementary data are available at *Age and Ageing* online.

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Conflicts of interest

None declared.

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