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Interaction between Obstructive Sleep Apnea and Shortened Telomere Length on Brain White Matter Abnormality

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Study Objectives: Age-related brain white matter changes (WMC) have been associated separately with obstructive sleep apnea (OSA) and short telomere length (TL). No studies have examined their interaction effect on WMC.

Methods: This is a cross-sectional study with a community-based sample of 420 participants (mean age, 61.3 ± 7.2) from the Korean Genome and Epidemiology Study during 2011–2012. An overnight fasted blood sample was taken to determine glucose and blood lipid levels at the sleep laboratory of Korea University Ansan Hospital. The status of brain WMC was determined using structural magnetic resonance imaging at 1.5 Tesla. Overnight polysomnography was performed, and leukocyte TL was measured. OSA was determined based on apnea-hypopnea index, and short TL was defined as the lowest quartile of the study participants.

Results: Adjusting for age, sex, BMI, smoking, drinking, snoring, and hypertension, odds ratio (OR) of brain WMC was estimated using multivariate logistic regression. The odds ratio was significant for cardiovascular disease (OR, 4.5; 95% CI, 1.2–16.3) and OSA (OR, 4.0; 95% CI, 1.0–15.2) among those with short TL; and for diabetes (OR, 3.0; 95% CI, 1.3–13.0) and age (OR, 1.1; 95% CI, 1.0–1.1) among those with longer TL. Interaction effect of OSA and short TL (OR, 4.3; 95% CI, 1.4–13.8) was significant, compared to those neither of them.

Conclusions: This study provides a first evidence of mediated interaction of short TL with OSA on brain WMC in a community-based sample. The results generate new hypotheses regarding mechanisms of impaired brain health in sleep apnea.

Keywords: brain white matter changes, sleep-disordered breathing, telomere shortening

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Significance

Reduced telomeres are related to ageing and oxidative stress, reported as a biomarker of age-related brain white matter changes. In a community-based cohort aged 50–79 years, age-related brain white matter abnormality was significant for those with both obstructive sleep apnea and shortened telomeres. Possible pathological pathways for telomere length in those with sleep disordered breathing may need to be examined relating to brain white matter changes.

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing in middle and older aged individuals. It is characterized by recurrent episodes of total or partial obstruction of the upper airway (apnea or hypopnea) during sleep. Snoring, fragmented sleep, repetitive hypoxemia/hypercapnia, daytime sleepiness, and cardiovascular complications are the associated features of OSA.[1,2] Magnetic resonance imaging (MRI) has shown that severe OSA is associated with structural brain changes, and OSA is considered a risk factor for decreased neurocognitive function, and an elevated risk of stroke and dementia.[3–8]

There is a growing body of literature suggesting that shortened telomere length (TL) is a candidate biomarker of ageing.[9] Telomeres form the end parts of eukaryotic chromosomes, consisting of tandemly repeated short stretches of DNA (TTAGGG in humans) and associated nucleoproteins.[10] Shortened TL is associated with cerebral subcortical atrophy and white matter hyperintensities.[10] An association of shortened TL with sleep apnea has also been reported.[11,12] However, to our knowledge, no prior studies have investigated whether OSA is related to the link of shortened TL to brain white matter changes. Sleep apnea might enhance oxidative stress by the reduction of antioxidant capacity of blood due to nocturnal hypoxia.[13] Oxidative stress may contribute to shorter telomeres via several potential pathways.[14] In addition, shortened TL indicates a senescent and inflammatory immune system, and this may possibly affect the brain, particularly among aged people.[15] Thus, using the two markers jointly for oxidative stress exposure would better account for the linkage to age-related brain white matter abnormality. Based on a community-based sample, we investigated whether the joint status of short TL and presence of OSA may be linked as a marker to brain white matter changes.

METHODS

Study Population

We studied participants enrolled in the Korean Genome and Epidemiology Study, a prospective biennial community-based study that was established with 5,020 residents in Ansan city, aged between 40 and 70 years in 2001. The cohort participants continue to have follow-up examinations on demographic characteristics, medical history, health standing, and sleep-related factors. From the study participants during 2011–2012, our analytic cohort comprised a total of 420 individuals who had complete information on the key measurements of polysomnography (n = 948), leukocyte TL (n = 2,314), and structural brain MRI (n = 1,074) in addition to the basic cohort examinations. The institutional review board of Korea University Ansan Hospital approved the study protocol (approval number: AS0624), and written informed consent was obtained from study participants.

Polysomnography

Participants underwent a standard overnight polysomnography using a comprehensive portable device (Embletta X-100; Embla Systems, Broomfield, CO, USA) at home or at the sleep laboratory onsite. Polysomnography result was scored by an experienced sleep technician following standard criteria.[16] Apneas (complete cessation of nasal and oral airflow) and hypopneas (discernible, > 30% reduction in airflow on nasal pressure trace) were scored if occurring for ≥ 10 s and accompanied by ≥ 4% reduction in oxyhemoglobin saturation. The OSA severity, based on the apnea-hypopnea index, was categorized as normal (< 5), mild (5–14.9), moderate (15–29.9), or severe (≥ 30).[17] Excessive daytime sleepiness was identified with a total score ≥ 10 using the Epworth Sleepiness Scale of 8 questions, each on a 4-point scale.[18]

Cerebral White Matter Changes Assessment

MRI was performed within an average of 2.3 days (standard deviation, 3.96) from polysomnographic monitoring. All scans were performed on a GE Signal HDxt 1.5T MRI scanner (GE Medical Systems, WI, USA) with an 8-channel head coil. White matter changes on MRI were identified with hyperintensities ≥ 5 mm on FLAIR images. It was rated as 0 for no lesion, 1 for focal lesion ≤ 10 mm, 2 for a beginning confluent lesion, and 3 for confluent lesion involving the entire region of each side of the hemispheres within the 5 predetermined standardized regions—frontal, parieto-occipital, temporal, basal ganglia, and infratentorial.[19] The total score, known to have a correlation with lesion volume,[20] was used to classify white matter changes to be none (0), mild (1–3), or moderate-or-severe (≥ 4).[21,22]

Leukocyte TL

Quantitative real-time polymerase chain reaction (qRT-PCR) was used to determine TL.[23] Genomic DNA was extracted from peripheral blood leukocytes using QIAamp DNA mini kit (QIAGEN, Germany). The ratio of the telomere repeat copy number to the single-copy gene (36B4 gene which encodes acidic ribosomal phosphoprotein) copy number, was determined for relative leukocyte telomere length (TL) by using the iQ Multi-Color Real-Time PCR Detection System (Bio-Rad, CA, USA). For the ratio of telomere to single-copy gene, the following telomere primers sequences were used:

- 5'-GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT-3' (forward),
- 5'-TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA-3' (reverse).

The PCR primer sequences for 36B4 were:

- 5'-CAGCAAGTGGGAAGGTGTAATCC-3' (forward),
- 5'-CCCATTCTATCATCAACGGGTACAA-3' (reverse).

Quantitative real-time polymerase chain reaction was performed using telomere and 36B4 primers in the same 96 well plate, and each plate included serial diluted reference DNA sample. The cycle threshold was transformed to DNA (ng) according to the standard curve of a serial diluted reference DNA obtained from the reactions between telomeres and the 36B4 gene. Relative leukocyte TL was validated with 25 samples, and the correlation coefficients of inter- and intra-reliability assays were 0.69 and 0.78, respectively.

Other Measures

All participants completed a questionnaire assessment of medical history and underwent a brief physical examination at visit for the study. Information on age, gender, height, weight, snoring, current and past status of drinking and smoking, diabetes, hypertension, cardiovascular disease, and cancers were included in the analyses as potential confounders. Body mass index was calculated as weight in kilograms divided by height in squared meters, and overweight and obese were determined by body mass index over 25 and 30, respectively. An overnight fasted blood sample was taken to determine glucose and blood lipid levels. Diabetes mellitus was identified based on the level of fasted blood glucose ≥ 126 mg/dL or use of medication. Systolic and diastolic blood pressures were measured 3 times with a sphygmomanometer, and the averages lower than 140 and 90 mm Hg, respectively, or use of antihypertensive medication were used to determine the presence of hypertension.

Statistical Analyses

TL was skewed to the right with a median of 0.98 (interquartile range, 0.83–1.20), and the lowest quartile (0.825) of the whole set of TL measurements (n = 2,314) was used to define short TL. The study participants were from the general population, and there were only three individuals with moderate-or-severe white matter changes, particularly among those with OSA and short TL. Thus, the mild and moderate-or-severe levels of white matter changes were combined to define white matter abnormality, and it was compared to those without white matter changes. Pearson χ^2 test was used in univariate analyses with baseline characteristics, and potential risk factors for white matter changes were identified. Significant level of OSA severity in association with brain white matter abnormality was identified in a stratified analysis. Effect sizes of OSA, short TL, and their concurrent joint condition were estimated with odds ratios without adjustment.[24] Adjusting for the factors identified significant from the univariate analyses, odds ratio of white matter abnormality was estimated relating to OSA, short TL, and their interactions defined as a multiplicative interaction. All statistical analyses were done using SPSS (IBM Statistics, version 20) with the 0.05 level of significance.

RESULTS

Baseline Characteristics and Prevalence of White Matter Abnormality

A total of 420 participants were analyzed with complete information on the key variables for the present study. Among them, 124 of 192 brain white matter abnormalities were mild changes and 68 were moderate or severe changes. The overall mean age of the study participants was 61.3 years (standard deviation, 7.2) with more females (59.5%). Compared to those without white matter changes (Table 1), individuals with white matter abnormality were older in mean age (63 vs. 58 years; P < 0.001), and had higher body mass index (median, 25.3 vs.

24.5 kg/m^2; P < 0.05), systolic blood pressure (117 vs. 112 in mm Hg; P < 0.001), and apnea-hypopnea index (median, 5.8 vs. 3.3; P < 0.001), respectively. They were not significantly different in TL, diastolic blood pressure, and excessive daytime sleepiness. Among individuals having brain white matter changes were more males (46.4% vs. 35.5%; P < 0.05), and more smokers (38% vs. 27.6%; P < 0.05). Also, they had more hypertension (46.4% vs. 23.7%, P < 0.001), diabetes mellitus (21.4% vs. 8.3%, P < 0.001), and cardiovascular disease (20.3% vs. 10.5%, P < 0.05).

Brain White Matter Abnormality and OSA Severity

In the stratified analysis by OSA severity (Table 2), white matter changes among those with short TL were significant among those with moderate or severe OSA (odds ratio [OR], 6.3; 95% CI, 2.0–19.6) but not among those with mild OSA, compared to normal individuals without OSA (AHI < 5). On the other hand, white matter changes among longer TL were not significant regardless of OSA severity. In all with short or longer TL, white matter changes were significant not among mild OSA, but among moderate-or-severe OSA (OR, 2.7; 95% CI, 1.5–5.0), compared to those without OSA (AHI < 5).

In addition, an ordinal association of white matter changes with OSA was examined over their severities, but no significance was found with Kendall tau-b (P values: 0.082 for all, 0.089 for short TL, and 0.351 for longer TL).

Effect Sizes between Groups

The effect size of OSA on white matter abnormality was > 2 to indicate medium (OR, 2.53; 95% CI, 1.43–4.47), and the effect size of short TL was < 1.5 to indicate none (OR, 1.34; 95% CI, 0.89–2.01). The effect size of the concurrent condition of OSA with short TL was even greater than 3 to indicate large (OR, 6.55; 95% CI, 2.20–19.52). Thus, the concurrent condition of OSA with short TL made a better prediction of white matter abnormality than OSA or short TL alone.

Table 1—Baseline characteristics by white matter abnormality status (n = 420).

Characteristic	White Matter Abnormality Yes (n = 192)	White Matter Abnormality No (n = 228)	P value
Age, year			< 0.001*
Median	63	58	
Mean (SD)	63.5 (7.2)	59.4 (6.7)	
Male, n (%)	90 (46.4)	81 (35.5)	0.024*
Body mass index, kg/m^2			
Median	25.3	24.5	0.041*
Mean (SD)	25.1 (3.2)	24.5 (2.8)	
Underweight, n (%)	1 (0.5)	1 (0.4)	
Overweight, n (%)	93 (48.2)	94 (41.2)	
Obese, n (%)	10 (5.2)	8 (3.5)	
Systolic blood pressure, mm Hg			< 0.001*
Median	117	112	
Mean (SD)	119.4 (14.2)	114.2 (13.7)	
Diastolic blood pressure, mm Hg			0.302
Median	74	73	
Mean (SD)	74.6 (9.1)	73 (9.0)	
Hypertension, n (%)	90 (46.4)	54 (23.7)	< 0.001*
Diabetes mellitus, n (%)	41 (21.4)	19 (8.3)	< 0.001*
Cardiovascular disease, n (%)	39 (20.3)	24 (10.5)	0.005*
Cancers, n (%)	2 (1.0)	1 (0.4)	0.465
Drinking, n (%)	86 (44.3)	91 (39.9)	0.367
Current drinking, n (%)	67 (34.9)	79 (34.6)	0.958
Smoking, n (%)	73 (38.0)	63 (27.6)	0.023*
Current smoking, n (%)	17 (8.9)	17 (7.5)	0.601
Habitual snoring, n (%)	47 (24.5)	45 (19.7)	0.242
Epworth Sleepiness Scale, score			0.570
Median	4	4	
Mean (SD)	4.2 (2.8)	4.3 (2.6)	
AHI, events/h			< 0.001*
Median (IQR)	5.8 (9.8)	3.3 (7.4)	
Mean (SD)	8.7 (9.3)	6.0 (5.8)	
Leukocyte telomere length			0.270
Median (IQR)	0.9 (0.3)	0.9 (0.4)	
Mean (SD)	1.0 (0.5)	1.0 (0.4)	

*Significant at the 0.05 level based on Kruskal-Wallis rank test or Pearson χ^2 test.
SD, standard deviation; AHI, apnea-hypopnea index.

Adjusted Odds Ratios of White Matter Abnormality without Interaction

Adjusting for age, sex, body mass index, systolic blood pressure, smokers, drinking, snoring, hypertension, diabetes, and cardiovascular disease that were significant in univariate analyses (Table 1), odds ratio of white matter abnormality was found to be significant for moderate-or-severe OSA, but only among those with short TL (OR, 4.0; 95% CI, 1.0–15.2), not among those with longer TL. Among those with short TL, white matter abnormality risk significantly increased in those with cardiovascular disease (OR, 4.5; 95% CI, 1.2–16.3) and smokers (OR, 6.3; 95% CI, 1.5–25.9). On the other hand, in those with longer TL, the risk of white matter abnormality increased with aging (OR, 1.1; 95% CI, 1.0–1.1) and for those with diabetes mellitus (OR, 1.3; 95% CI, 1.3–6.8).

Interaction Effect between OSA and Short TL on White Matter Abnormality

For all the participants, 4-level interactions between moderate-to-severe OSA (yes/no) and short TL (yes/no) were examined for their effects on white matter abnormality adjusting for age, sex, body mass index, systolic blood pressure, smokers, drinking, snoring, hypertension, diabetes, and cardiovascular disease (Table 4). The odds ratio was significant relating to the concurrent condition of moderate-to-severe OSA with short TL (OR, 4.3; 95% CI, 1.4–13.8), but not significant relating to only one of these conditions, respectively compared to the reference condition without OSA with longer TL. The adjusted odds ratio relating to the binary interaction defined for the concurrent joint condition of OSA with short TL versus the other 3 joint conditions in all was consistently significant (OR, 4.2; 95% CI,

Table 2—Odds ratios of brain white matter abnormality at various levels of OSA Severities as compared to normal individuals without adjustment.

TL	OSA (AHI)	White Matter Abnormality, n (%) Yes	No	Odds Ratio (95% CI)	P value
Short TL [a]		73 (50.7)	71 (49.3)		0.004*
	Normal (< 5)	31 (40.8)	45 (59.2)	Reference	
	Mild OSA (5–14.9)	22 (50.0)	22 (50.0)	1.5 (0.7–3.1)	> 0.05
	Moderate-to-severe OSA (≥ 15)	20 (83.3)	4 (16.7)	6.3 (2.0–19.6)	< 0.001*
	Moderate OSA (15–29.9)	17 (81.0)	4 (19.0)	6.2 (1.9–20.1)	0.001*
	Severe OSA (≥ 30)	3 (100.0)	0 (0.0)	2.5 (1.9–3.2)	0.042*
Longer TL		119 (43.1)	157 (56.9)		> 0.05
	Normal (< 5)	59 (39.6)	90 (60.4)	Reference	
	Mild OSA (5–14.9)	41 (45.1)	50 (54.9)	1.3 (0.7–2.1)	> 0.05
	Moderate-or-severe OSA (≥ 15)	19 (52.8)	17 (47.2)	1.6 (0.8–3.2)	> 0.05
	Moderate OSA (15–29.9)	18 (54.5)	15 (45.5)	1.8 (0.9–3.9)	> 0.05
	Severe OSA (≥ 30)	1 (33.3)	2 (66.7)	Not applicable	
All					
	Normal (< 5)	90 (40.0)	135 (60.0)	Reference	
	Mild OSA (5–14.9)	63 (46.7)	72 (53.3)	1.3 (0.9–2.0)	> 0.05
	Moderate-or-severe OSA (≥ 15)	39 (65.0)	21 (35.0)	2.7 (1.5–5.0)	0.001*

[a] Less than 0.825. *Significant at the 0.05 level by Pearson χ^2 test. TL, telomere length; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; CI, confidence interval.

Table 3—Effect sizes of OSA, short TL, and their interaction on brain white matter changes.

Effect [a]	Odds Ratio (95% CI)	Effect Size [b]	P value
OSA (AHI ≥ 15)	2.53 (1.43–4.47)	Medium	0.001*
STL	1.34 (0.89–2.01)	Small	0.159
OSA × STL	6.55 (2.20–19.52)	Large	0.001*

[a] OSA is moderate or severe (AHI ≥ 15); STL is TL less than 0.825; OSA × STL is a binary interaction of OSA and STL. [b] Small 1.5, medium 2, and large 3 (Reference: Sullivan and Feinn 2012).[24] OSA, obstructive sleep apnea; STL, short telomere length; AHI, apnea-hypopnea index; CI, confidence interval.

1.4–13.3). In the model with binary interaction, age (OR, 1.1; 95% CI, 1.0–1.1) and hypertension (OR, 2.0; 95% CI, 1.3–3.2) were also significant to increase the risk of white matter abnormality.

Stepwise variable selection was applied at the 0.05 and 0.10 levels of significance for entry and removal, diabetes mellitus (OR, 2.0; 95% CI, 1.1–3.7) appeared to be significant to increase the risk of white matter abnormality, in addition to age (OR, 1.1; 95% CI, 1.0–1.1), hypertension (OR, 2.2; 95% CI, 1.4–3.4), and the concurrent joint condition of moderate-or-severe OSA with short TL (OR, 4.6; 95% CI, 1.5–14.1).

DISCUSSION

Consistent with a previous study,[25] we observed a significant association between brain white matter abnormality and moderate or greater severities of OSA in a community-based cohort of aged people 50–79 years. In addition, we in this study classified short TL as the first quartile range of the whole TL measurements with 2,314 individuals, and found an increased risk of brain white matter abnormality in the presence of OSA among those with short TL, but not among those with longer TL, adjusting for potential risk factors including age, cardiovascular disease, diabetes mellitus, hypertension, snoring, sex, smoking, and drinking. To our knowledge, the interaction effect on the risk of white matter changes is novel.

Telomeres shorten at every cell division, and the cell stops dividing once the shortest telomere reaches a critical length.[26] The rate of telomere shortening is accelerated when cells are exposed to genotoxic stresses (e.g. reactive oxygen species).[27] Intermittent hypoxia in OSA can induce mitochondrial dysfunction and thereby increases oxidative stress.[28] Further mechanisms may be metabolic stress induced by intermittent hypoxia, activation of inflammation pathways, and hemodynamic stress from nocturnal hypertension.[29–31] Reduced telomeres have been related to aging and oxidative stress, and reported as a biomarker, particularly of age-related brain white matter changes. In the present study, possible confounding factors including age were adjusted, but, a strong association of age-related brain white matter changes with the concurrent joint condition of OSA with short TL remained.

Studies have discussed of the mechanisms of cardiovascular disease in accelerated aging syndromes[32] and the roles of senescence and telomere shortening in cardiovascular disease.[33] Consistent with them, we observed a significant age-related white matter abnormality among those with cardiovascular disease particularly in those with short TL, but not with longer TL. Further studies may be of interest to investigate the extent of white matter abnormality with respect to different levels of inflammation associated with OSA among those with short TL. We found among longer TL that there was a significant increase of white matter abnormality in those with diabetes. Although

brain imaging in patients with diabetes in elderly people has been examined in many studies,[34,35] no studies have discussed a possible pathological pathway yet relating to telomere length.

Our community-based cross-sectional study had objective measures of sleep-disordered breathing based on apnea-hypopnea index, an estimation of brain white matter changes based on MRI, and a relatively unique alignment of data with TL. However, there are some study limitations that may warrant further investigation. First, we in this study collected polysomnography data at home or at sleep laboratory on-site for a single night; thus variability in sleep disturbance measures over time and over different estimation sites were not captured, and misclassification bias may be possible. However, several studies indicated measurements taken over one night or multiple nights at home or in laboratory are reliable.[36,37] The study participants were from the general population, and the number of individuals for severe OSA among moderate-to-severe white matter changes was limited. Lastly, our study cohort was community-based with one ethnicity from the general population of Korea, thus the findings may not be generalizable for ethnically diverse populations. Study finding for the associated risk of white matter changes with OSA and short TL may be a reasonable evidence to pose a clinical importance of early identification and treatment of OSA for brain white matter changes in aged people.

CONCLUSIONS

Prior investigations have reported an increased risk of brain white matter changes in aged people with OSA, and reduced TL linked to age-related brain white matter changes, but little has been discussed about OSA in the link. We found in a general population aged 50–79 years that OSA had a significant interaction with short TL, increasing the risk of brain white matter changes. Oxidative stress related to hypoxia may be one of the underlying mechanistic explanations for both shortened TL and OSA, thus a mediated interaction on white matter abnormality. The public health impact of intervention strategies for age-related white matter disease in brain such as mild cognitive impairment or dementia may benefit from early diagnosis and treatment of OSA.

ABBREVIATIONS

AOR, adjusted odds ratio
CI, confidence Interval
MRI, magnetic resonance imaging
TL, telomere length
OR, odds ratio
OSA, obstructive sleep apnea

Table 4—Estimated odds ratios of brain white matter abnormality relating to the presence of moderate-to-severe obstructive sleep apnea and short TL.

TL	Effect	Odds Ratio (95% CI)[a]	P value
Short TL without interaction	Age, years	1.1 (1.0–1.1)	0.119
	Hypertension	0.9 (0.1–6.4)	0.897
	Diabetes mellitus	0.8 (0.3–2.4)	0.669
	Sex	0.9 (0.2–3.3)	0.881
	CVD	4.5 (1.2–16.3)	0.024*
	Smoker	6.3 (1.5–25.9)	0.010*
	BMI, kg/m^2	1.1 (1.0–1.3)	0.066
	OSA[b]	4.0 (1.0–15.2)	0.044*
Longer TL without interaction	Age, years	1.1 (1.0–1.1)	0.000*
	Hypertension	3.6 (1.0–13.0)	0.055
	Diabetes mellitus	3.0 (1.3–6.8)	0.009*
	Sex	1.0 (0.4–2.3)	1.000
	CVD	0.9 (0.4–2.0)	0.884
	Smoker	0.7 (0.3–1.7)	0.490
	BMI, kg/m^2	1.0 (0.9–1.1)	0.647
	OSA[b]	1.2 (0.6–2.8)	0.596
All TL four-level interaction	Age, years	1.1 (1.0–1.1)	0.000*
	Hypertension	2.9 (1.0–8.6)	0.049*
	Diabetes mellitus	1.9 (1.0–3.6)	0.055
	Sex	1.1 (0.6–2.2)	0.746
	CVD	1.4 (0.8–2.6)	0.285
	Smoker	1.3 (0.6–2.5)	0.505
	BMI, kg/m^2	1.0 (1.0–1.1)	0.634
	Interaction: OSA[b] × TL (yes or no) × (short or longer)		
	(yes) × (short)	4.3 (1.4–13.8)	0.013*
	(yes) × (longer)	1.1 (0.7–1.8)	0.680
	(no) × (short)	1.1 (0.5–2.4)	0.806
	(no) × (longer)	Reference	
All TL binary interaction	Age, years	1.1 (1.0–1.1)	0.000*
	Hypertension	2.0 (1.3–3.2)	0.003*
	Diabetes mellitus	1.8 (1.0–3.5)	0.059
	Sex	1.1 (0.6–2.3)	0.708
	CVD	1.4 (0.7–2.5)	0.306
	Smoker	1.3 (0.6–2.5)	0.507
	BMI, kg/m^2	1.0 (0.9–1.1)	0.581
	OSA with short TL[c]	4.2 (1.4–13.3)	0.012*
All TL binary interaction with stepwise selection	Age, years	1.1 (1.0–1.1)	0.000*
	Hypertension	2.2 (1.4–3.4)	0.000*
	Diabetes mellitus	2.0 (1.1–3.7)	0.035*
	OSA with short TL[c]	4.6 (1.5–14.1)	0.008*

[a] Adjusted for age, sex, body mass index, smoking, hypertension, diabetes mellitus, and CVD. [b] Moderate-to-severe OSA (AHI ≥ 15). [c] Binary interaction of moderate-or-severe OSA and short TL referenced to the others altogether. *Significant at the 0.05 level. TL, telomere length; OSA, obstructive sleep apnea; CVD, cardiovascular disease; CI, confidence interval.

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