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SLEEP DISORDERED BREATHING

Association between Snoring and Leukocyte Telomere Length

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Study Objectives: Data on the association between snoring and telomere length, an indicator of biological aging, are very limited. Moreover, no polysomnography (PSG) studies on this association in a general population have been conducted. Our study aimed to evaluate the association between snoring and leukocyte telomere length (LTL) using PSG and a questionnaire.

Methods: A cross-sectional PSG study embedded in a population-based cohort from the Korean Genome Epidemiology Study was conducted in 2010–2013. During the same period, questionnaire-based interviews, blood collection, and relative LTL assays were conducted. A total of 887 Korean men and women aged 50–79 y with an apnea-hypopnea index (AHI) < 15 determined in the PSG study were included in the study.

Results: We observed that the percentage of time spent snoring during sleep (% time spent snoring) assessed by PSG was inversely associated with LTL even after adjusting for potential risk factors and AHI. In the linear regression association between tertiles of percentage of time spent snoring and log-transformed LTL, coefficient estimates (P value) were −0.076 (< 0.05) for the second tertile and −0.084 (< 0.01) for the third tertile compared with the bottom tertile. When LTL was compared according to snoring status determined using PSG and questionnaire information, both primary snorers and those with mild sleep apnea (5 ≤ AHI < 15) had shorter LTL than nonsnorers.

Conclusions: Our findings suggest that snoring may influence telomere attrition independent of sleep apnea.

Keywords: population-based study, leukocyte telomere length, polysomnography, snoring

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Significance

Leukocyte telomere length (LTL), which is increasingly used as a biomarker of cellular aging, is reportedly associated with chronic disease risk and mortality. Various studies have provided evidence that sleep-disordered breathing increases the risk of cardiovascular disease, diabetes mellitus, and hypertension. In addition, a small number of studies have shown a significant association between sleep apnea and LTL. However, data regarding the association between primary snoring and LTL are limited, and significant findings for this association have not yet been reported. The present study, which conducted polysomnographic and questionnaire-based assessments to measure snoring duration and frequency, provides evidence that snoring is significantly associated with shorter LTL independent of sleep apnea and suggests the potential effects of snoring on aging process.

INTRODUCTION

A limited number of studies have reported on the association between sleep disordered breathing (SDB) and telomere length,[1–3] which is considered a marker of biological aging. Two studies reported an inverse association between sleep apnea and telomere length in adults.[1,2] Although the mechanisms underlying this association have yet to be fully clarified, increased oxidative stress and an inflammatory response caused by sleep apnea have been suggested as potential mediators for telomere attrition.[1,2,4] Habitual snoring is a feature of SDB, which occurs commonly in the general population. Primary snoring is defined as the presence of snoring noises during sleep without episodes of apnea or arousals, whereas apneic snoring is accompanied by obstructive sleep apnea (OSA).[5] A recent study reported enhanced inflammatory stress in children with primary snoring.[6] Mechanical stress caused by repeated snoring vibrations and airway pressure gradients may increase regional inflammation.[7–9] Although no study has reported on the direct association between primary snoring and systemic inflammation, some indirect evidence suggests their possible association.[10,11] There may also be possible effects of mechanical stress on cellular injury and death. Given these mechanisms, primary snoring is thought to influence telomere attrition. However, it was not significantly associated with telomere length in a previous study.[2] Because that study only included a small number of primary snorers, it might have lacked sufficient statistical power to detect such an association.[2] Because only a single study to date has reported an association between primary snoring and telomere length, further studies on the topic are warranted.

In this study, we examined the association between subjective and objective assessments of snoring and leukocyte telomere length (LTL). The subjective assessment included reports on snoring frequency through a questionnaire-based interview, whereas the objective assessment consisted of a polysomnography (PSG) evaluation of snoring. In particular, we attempted to investigate these associations in individuals with an apnea-hypopnea index (AHI) < 15 in the PSG evaluation to minimize the effects of sleep apnea. As in previous studies,[1–3] we used LTL as an indicator of telomere length because the attrition rates of telomere length in leukocytes and other somatic cells are considered similar.[12]

METHODS

Study Design and Population

We performed this cross-sectional study of a population-based cohort included in the Korean Genome Epidemiology Study, an ongoing prospective study. Detailed information on the study procedures is available elsewhere.[13,14] Briefly, 5,015 cohort members (Korean male and female residents of Ansan who were 40–69 y of age at baseline) were enrolled between June 18, 2001 and January 29, 2003. At baseline, all study participants completed a comprehensive health examination and an on-site interview at the Korea University Ansan Hospital. Follow-up examinations and interviews were conducted

biennially during a scheduled site visit. The health examination consisted of anthropometric, biochemical, and clinical evaluations including chest radiography, pulmonary function test, electrocardiography, echocardiography, carotid ultrasonography, computed tomography, ophthalmic examination, and dental examination. In the interview, participants answered a questionnaire to provide demographic information as well as data on their medical history, family disease history, health conditions, and lifestyle. Among all cohort members, 1,364 participants underwent PSG and provided biospecimens between January 2010 and February 2013. Of these study participants, we excluded those who showed outlying LTL values or who received a diagnosis of cancer, cardiovascular disease, or diabetes mellitus (n = 343). We also excluded those with a diagnosis of moderate or severe OSA as determined in the PSG evaluation (n = 134). The data of 887 participants were ultimately included in the final analysis.

The Human Subjects Review Committee of Korea University Ansan Hospital approved the study protocols. Each participant signed an informed consent form at every site visit.

Leukocyte Telomere Length Measurement

Peripheral blood samples were collected and immediately frozen in dry ice prior to storage at −80°C. Within 2 mo of storage, leukocyte genomic DNA was extracted from the samples using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Purified DNA samples were diluted and quantified using a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). Relative LTL was measured using quantitative real-time polymerase chain reaction.[15] The ratio of the telomere repeat copy number to the single-copy gene (36B4 gene encoding acidic ribosomal phosphoprotein) copy number was determined to assess the relative LTL using the iQ Multi-Color Real-Time Polymerase Chain Reaction Detection System (Bio-Rad, Hercules, CA, USA). The final concentrations of the polymerase chain reaction reagents were 1xSYBR Green SuperMix (Bio-Rad), 50 ng of DNA, 0.2 μM telomere primers (forward, 5′-GGTTTTTGAGGGTGAGGGTGAGGGTGAGGGTGAGGGT-3′; reverse, 5′-TCCCGACTATCCCTATCCCTATCCCTATCCCTATCCCTA-3′), and 0.3 μM 36B4 primers (forward, 5′-CAGCAAGTGGGAAGGTGTAATCC-3′; reverse, 5′-CCCATTCTATCATCAACGGGTACAA-3′). The reactions were performed using telomere and 36B4 primers in the same 96-well plate, and each plate included a reference DNA sample. A four-point standard curve was established to transform the cycle threshold into nanograms of DNA. A validity test showed that the Pearson correlation coefficients were 0.78 for intra-assay and 0.69 for interassay when 25 samples were run in triplicate.

Snoring and Apnea Assessment

In the questionnaire-based interview, the participants were asked to report on snoring status during sleep (no snoring or snoring). Furthermore, snorers were asked how frequently they snored (infrequently, one to four times a week, four to five times a week, six to seven times a week). A test-retest reliability study found substantial agreement for the question about snoring.[16]

We conducted an unattended overnight PSG either at the patient's home or at the sleep laboratory of the Korea University Ansan Hospital using a portable monitoring device (Embletta X-100; Embla Systems, Broomfield, CO, USA). This device has channels for electroencephalogram, electrooculogram, chin muscle electromyogram, electrocardiogram, a pressure transducer airflow sensor, a chest and abdominal respiratory movement sensor, a snore sensor, and a pulse oximeter. A trained sleep technologist connected the device to the patient at bedtime, collected an unattended overnight recording the following morning, and manually scored the PSG results according to standard criteria.[17] Apnea was defined as a > 90% reduction in airflow from baseline for at least 10 sec, whereas hypopnea was defined as a ≥ 30% reduction in airflow from baseline accompanied by a ≥ 4% decrease in oxygen saturation. We obtained AHI, the average number of apnea and hypopnea events per sleep hour, as well as the oxygen desaturation index. Based on the AHI, no OSA (< 5), mild OSA (5–14.9), moderate OSA (15–29.9), and severe OSA (≥ 30) were determined. Snoring was detected by a nasal cannula in conjunction with a pressure sensor, which monitors the pressure fluctuations produced by snoring. Snoring episodes with values > 20 μbar were recorded after excluding artifacts ≥ 10,000 μbar. We obtained the cumulative duration of snoring episodes from the data record and calculated the percentage of time spent snoring during sleep (% time spent snoring) by dividing the cumulative duration of snoring episodes by the total sleep time.

Using the PSG-derived snoring information and questionnaire results, snoring status was classified into nonsnorers, primary snorers without OSA (AHI < 5), and snorers with mild OSA (5 ≤ AHI < 15). Nonsnorers were defined as individuals who reported "no or infrequent snoring" in the questionnaire and whose % time spent snoring was < 3% (median) based on the PSG evaluation. Snorers were defined as those who reported "snoring ≥ 1 nights/w" or whose % time spent snoring was ≥ 3%.

Confounding Factors

Information on the participants' age, sex, smoking status, alcohol consumption, physical activity, and medication use for the treatment of hypertension or dyslipidemia was collected in the questionnaire-based interviews. Physical activity was assessed using a scale consisting of five categories for activity intensity as measured by hours spent in a typical day per level of intensity. A total metabolic equivalent (MET/h) score was calculated by multiplying the hours spent at a particular activity intensity by MET value (1.0 for sleep or sedentary, 1.5 for very light, 2.4 for light, 5.0 for moderate, and 7.5 for vigorous activity), which were determined based on examples of activities given for each category. The presence of hypertension or dyslipidemia was determined based on blood pressure (BP) and biochemical indicators as measured in the health examination as well as medication information. BP was measured in the sitting position with mercury sphygmomanometers after a rest period of at least 5 min. Repeated BP measurements were performed in an approximately 30-sec interval and recorded to the nearest 2 mmHg. The average of two measurements was calculated for systolic and diastolic BP. Blood samples were collected after a fasting period of at least 8 h. Total cholesterol, high-density

lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured in a commercial laboratory (Seoul Clinical Laboratories, Seoul, Korea). The following diagnostic criteria were employed: use of antihypertensive medications or having systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg for hypertension; use of hypolipidemic medications or having serum total cholesterol levels ≥ 240 mg/dL, serum triglyceride levels ≥ 150 mg/dL, or serum HDL-cholesterol levels < 50 mg/dL (women) or < 40 mg/dL (men) for dyslipidemia. Anthropometric data were collected through a comprehensive health examination conducted by health professionals according to a standardized protocol. Height (cm) and body weight (kg) were measured to the nearest 0.1 cm or 0.1 kg without footwear and the body mass index (BMI, kg/m^2) was calculated. Obesity was defined as a BMI of 25 kg/m^2 as a cutoff point for Asian populations.

Statistical Analysis

To evaluate the association between snoring and LTL, LTL was transformed using the natural logarithm function to minimize the effect of outliers and fitted as a dependent variable for linear regression analysis. As independent variables, three snoring frequency groups (no or infrequent snoring, 1 to 3 nights/w, and ≥ 4 nights/w) and tertiles of % time spent snoring were used. In the multiple models, potential confounding variables such as age (continuous), sex, BMI (continuous), smoking status (nonsmoker versus smoker), alcohol consumption (nondrinker versus drinker), and physical activity (quintiles of MET/h/d) as well as the presence of hypertension or dyslipidemia were included as covariates. In addition, AHI was further adjusted for with other confounding variables. A joint analysis for % time spent snoring and risk factors of snoring, such as age, sex, obesity, smoking, and alcohol consumption, was conducted using similar multiple linear regression models. Furthermore, LTL was compared among the three snoring status groups (nonsnorers, primary snorers, and snorers with mild OSA) using analysis of variance and Scheffé *post hoc* tests. All statistical analyses were performed using SAS software (SAS 9.1.3; SAS Institute, Cary, NC, USA).

RESULTS

The characteristics of the study participants are shown in Table 1. LTL was observed between 0.09 and 10.2, and % time spent snoring was 0–72%. Chronological age was inversely correlated with LTL ($P < 0.001$) and % time spent snoring ($P < 0.01$).

Table 2 shows the association of snoring (questionnaire- and PSG-based snoring variables) and LTL. Only age was adjusted for in model 1, whereas age and other confounding variables were adjusted for in model 2. In model 3, in which AHI was further adjusted for, the association between % time spent snoring from PSG and LTL was significant; compared with the bottom tertile, the second and third tertiles were inversely associated with LTL ($P < 0.05$ and < 0.01, respectively). However, habitual snoring (≥ 4 nights/w) reported in the questionnaire was not significantly associated with LTL, although an inverse trend was seen compared with no or infrequent snoring.

As shown in Figure 1, primary snorers and snorers with mild OSA showed a shorter LTL than nonsnorers ($P < 0.05$),

Table 1—Characteristics and polysomnography recording data of the study population (n = 887).

	Descriptive Statistics
Leukocyte telomere length	1.09 ± 0.53
Age, y	58.9 ± 7.1
Male sex, %	47.9
Body mass index, kg/m^2	24.3 ± 2.7
Current smoker, %	11.8
Current alcohol drinker, %	46.0
Physical activity, MET/h	41.1 ± 7.3
Presence of hypertension, %	29.0
Presence of dyslipidemia, %	50.7
Reported snoring frequency, %	
No or infrequent snoring	74.4
1–3 nights/w	6.9
4–7 nights/w	18.7
Polysomnographic recordings	
Total sleep time, min	395.0 ± 77.1
Time spent snoring, min	30.5 ± 44.1
Percentage of time spent snoring	7.8 ± 11.1
Number of snoring episodes	37.5 ± 43.0
AHI, events/h	4.3 ± 3.9
AHI < 5 events/h, %	66.0
5 ≤ AHI < 15 events/h, %	34.0
Oxygen desaturation index, events/h	3.8 ± 3.6
Minimum oxygen saturation, %	88.6 ± 4.1

Values presented as mean ± standard deviation or percent as indicated.
AHI, apnea-hypopnea index; MET, metabolic equivalent.

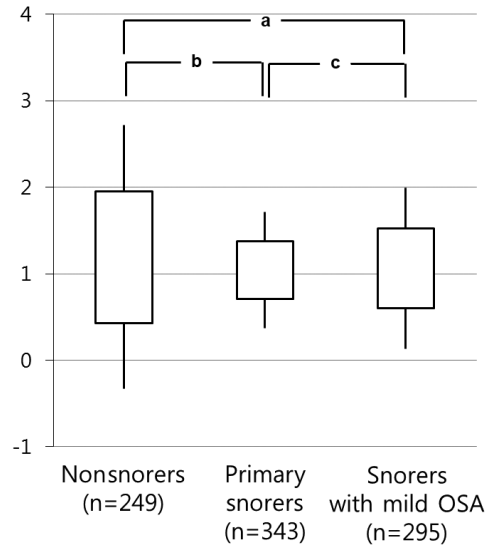

Figure 1—Boxplot of leukocyte telomere length for nonsnorers, primary snorers, and snorers with mild obstructive sleep apnea (OSA). In the boxplot, the range of a box indicates mean ± standard deviation (SD) and the range of whiskers for each box indicates mean ± 2 SD. [a] $P < 0.05$, [b] $P < 0.05$, [c] $P = 0.99$. P values were obtained from multiple comparison tests (Scheffé's method) between groups after adjustment for age, sex, body mass index, smoking status, alcohol consumption, physical activity, and diagnosis of hypertension or dyslipidemia.

Table 2—Association between snoring and leukocyte telomere length.

Snoring Assessment	Category	Coefficient Estimate ± SE for LTL (P value)[a]		
		Model 1	Model 2	Model 3
Questionnaire-based report Snoring frequency	No or infrequent snoring	Reference	Reference	Reference
	1–3 nights/w	−0.045 ± 0.049 (0.36)	−0.037 ± 0.049 (0.46)	−0.038 ± 0.049 (0.44)
	≥ 4 nights/w	−0.058 ± 0.032 (0.070)	−0.050 ± 0.032 (0.12)	−0.059 ± 0.033 (0.076)
Polysomnographic assessment % time spent snoring	1st tertile	Reference	Reference	Reference
	2nd tertile	−0.073 ± 0.030 (0.015)	−0.073 ± 0.030 (0.017)	−0.076 ± 0.030 (0.012)
	3rd tertile	−0.083 ± 0.030 (< 0.01)	−0.075 ± 0.032 (0.019)	−0.084 ± 0.033 (< 0.01)

Model 1: Age was adjusted for. Model 2: Age, sex, body mass index, smoking status, alcohol consumption, physical activity, and diagnosis of hypertension or dyslipidemia were adjusted for. Model 3: Variables in the Model 2 and apnea-hypopnea index were adjusted for. [a] Log-transformed value. LTL, leukocyte telomere length; SE, standard error.

Table 3—Joint analysis of snoring and risk factors in the association with leukocyte telomere length.

Median % Time Spent Snoring	Risk Factor	n (%)	Coefficient Estimate ± SE for LTL (P value)[a]
< 3%	Age < 65 y	338 (38.1)	Reference
	Age ≥ 65 y	111 (12.5)	−0.066 ± 0.042 (0.12)
≥ 3%	Age < 65 y	365 (41.2)	−0.036 ± 0.029 (0.22)
	Age ≥ 65 y	73 (8.2)	−0.170 ± 0.049 (< 0.001)
< 3%	Female sex	292 (32.9)	Reference
	Male sex	157 (17.7)	0.033 ± 0.039 (0.40)
≥ 3%	Female sex	170 (19.2)	−0.027 ± 0.035 (0.44)
	Male sex	268 (30.2)	−0.052 ± 0.036 (0.15)
< 3%	BMI < 25 kg/m^2	297 (33.5)	Reference
	BMI ≥ 25 kg/m^2	152 (17.1)	−0.054 ± 0.037 (0.15)
≥ 3%	BMI < 25 kg/m^2	239 (26.9)	−0.058 ± 0.032 (0.08)
	BMI ≥ 25 kg/m^2	199 (22.5)	−0.097 ± 0.036 (< 0.01)
< 3%	Nonsmoker	413 (46.6)	Reference
	Smoker	36 (4.1)	0.013 ± 0.066 (0.85)
≥ 3%	Nonsmoker	369 (41.6)	−0.051 ± 0.028 (0.07)
	Smoker	69 (7.8)	−0.070 ± 0.052 (0.18)
< 3%	No alcohol consumption	279 (31.4)	Reference
	Alcohol consumption	170 (19.2)	−0.019 ± 0.037 (0.62)
≥ 3%	No alcohol consumption	200 (22.6)	−0.024 ± 0.034 (0.49)
	Alcohol consumption	238 (26.8)	−0.11 ± 0.038 (< 0.01)

Age, sex, body mass index, smoking status, alcohol consumption, physical activity, diagnosis of hypertension or dyslipidemia, and apnea-hypopnea index were adjusted for. [a] Log-transformed value. BMI, body mass index; LTL, leukocyte telomere length; SE, standard error.

but there was no significant difference in LTL between primary snorers and snorers with mild OSA.

Table 3 presents the results of joint analysis for % time spent snoring during sleep and risk factors of snoring, such as age, sex, obesity, smoking, and alcohol consumption, in the association with LTL. Using the median value of % time spent snoring as a cutoff point, combined groups of % time spent snoring (< 3% and ≥ 3%) with binary variables of age (< 65 y and ≥ 65 y), sex (male and female), BMI (< 25 kg/m^2 and ≥ 25 kg/m^2), smoking status (non-smoking and smoking), and alcohol consumption status (no consumption and consumption) were fitted in the multiple models. A higher percentage of time spent snoring (≥ 3%) was significantly associated with shorter LTL when combined with older age (≥ 65 y) ($P < 0.001$), obesity (≥ 25 kg/m^2) ($P < 0.01$), and alcohol consumption ($P < 0.01$).

DISCUSSION

We evaluated the presence of snoring using a questionnaire-based interview and an overnight PSG and assessed its associations with telomere length in this population-based cross-sectional study. A higher percentage of time spent snoring during sleep as identified by the PSG was significantly associated with a shorter LTL regardless of the presence of apnea. Here we report novel data on significantly shorter telomere length in primary snorers and snorers with mild OSA compared with nonsnorers. In this study, approximately 45% of the study participants classified as nonsnorers or infrequent snorers based on the questionnaire information were revealed by the PSG to snore for ≥ 10 min. These data suggest that individuals who are unaware of their snoring require objective evaluation by PSG to identify the presence of snoring.

Telomeres are regions of repetitive DNA sequences (TTAGGG) that protect the ends of chromosomes. Their length shortens gradually with every cell division and reflects cellular aging. This process is accelerated by oxidative and inflammatory stress, which damages DNA and cells.[18,19] The mechanism underlying the association between OSA and telomere attrition

has been explained by enhanced oxidative and inflammatory stress caused by OSA. OSA is characterized by intermittent hypoxia, which may induce the generation of reactive oxygen and nitrogen species and lead to the burden of oxidative stress and the production of inflammatory cells and molecules.[20] In addition, during OSA, augmented respiratory efforts against a closed airway induce intrathoracic pressure changes, which enhance systemic inflammation.[21] Two previous studies reported on the association between OSA and telomere length in adults.[1,2] One study showed that patients with OSA had shorter LTL than controls without OSA. However, the authors did not find a dose-response relationship between AHI and LTL.[1] The second study analyzed the association between a history of apnea or snoring and LTL in a birth cohort study and found that apnea showed a significant association with LTL, whereas primary snoring did not.[2] However, the number of primary snorers was very small in that study because only hospitalized cases were identified through medical records. Thus, the association between snoring and LTL could not reach significance due to a lack of statistical power.[2]

We postulate that the biological mechanisms underlying the association between primary snoring and telomere length may be mechanical and inflammatory stress associated with repeated vibratory stimuli during snoring. Mechanical trauma and inflammatory cytokine production are considered factors that cause pathological cellular damage.[22] To the best of our knowledge, however, no data to date have been reported on the direct effects of primary snoring on cell damage. There are few data on the effects of primary snoring on inflammatory stress. One previous study demonstrated that children with primary snoring had higher levels of serum resistin (an inflammatory biomarker) than nonsnorers.[6] Two experimental studies suggested that repeated snoring vibrations might trigger inflammation.[7,8] An in vitro study found that levels of interleukin-8 (a proinflammatory biomarker) were significantly elevated in the supernatant of a cell culture subjected to vibration stimuli simulating snoring.[7] In an in vivo study, snoring-like vibrations applied to rat models induced mRNA overexpression of inflammatory proteins in the soft-palate tissue.[8] However, these data indicated snoring-induced regional[7–9] but not systemic inflammation. One study showed that habitual snoring is associated with carotid atherosclerosis,[10] which is associated with systemic inflammation[11] as well as endothelial cell damage.[23]

The strengths of our study include that the data were derived from a general population, LTL measurements were taken of a large sample size, and both subjective and objective snoring assessments were used. However, our study also has some limitations. Because design was cross-sectional, a causal relationship between snoring and LTL could not be established. Moreover, our findings might not be generalizable to other ethnicities or younger age groups because the study participants were all Korean adults of middle age or older. AHI and the percentage of time spent snoring derived from PSG might be underestimated or overestimated by random errors because only a single-night PSG was conducted, and body position during sleep is reportedly one factor that can cause measurement errors in a single-night PSG.[24] Also, we were unable to compare the time spent snoring detected by a snore sensor used here with those in other detection methods such as a microphone recording of snoring sounds.

In summary, this cross-sectional study demonstrated that snoring was associated with telomere length independent of apnea. Further investigations of the biological mechanisms underlying this association are warranted.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
BP, blood pressure
HDL, high-density lipoprotein
LTL, leukocyte telomere length
MET, metabolic equivalent
OSA, obstructive sleep apnea
PSG, polysomnography
SDB, sleep disordered breathing

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