dmj
DIABETES & METABOLISM JOURNAL

Check for updates

Association of Snoring with Prediabetes and Type 2 Diabetes Mellitus: The Cardiovascular and Metabolic Diseases Etiology Research Center Cohort

So Mi Jemma Cho[1,2], Hokyou Lee[2,3], Jee-Seon Shim[4], Hyeon Chang Kim[2,4]

Departments of [1]Public Health, [2]Preventive Medicine, [3]Internal Medicine, [4]Cardiovascular and Metabolic Diseases Etiology Research Center, Yonsei University College of Medicine, Seoul, Korea

Background: Evidence suggests that habitual snoring is an independent risk factor for poor glycemic health. We examined the associations between snoring with prediabetes and diabetes in Korean population.

Methods: Self-reported snoring characteristics were collected from 3,948 middle-aged adults without prior cardiovascular diseases. Multivariable linear regression assessed the association of snoring intensity, frequency, disruptiveness, and disrupted breathing with fasting glucose and glycosylated hemoglobin (HbA1c) level. Then, multinomial regression evaluated how increasing snoring symptoms are associated with the risk for prediabetes and diabetes, adjusting for socioeconomic and behavioral risk factors of diabetes, obesity, hypertension, and other sleep variables.

Results: Higher snoring intensity and frequency were positively associated with fasting glucose and HbA1c levels. Participants presenting the most severe snoring were at 1.84 times higher risk (95% confidence interval [CI], 1.09 to 2.29) for prediabetes and 2.24 times higher risk (95% CI, 1.84 to 2.95) for diabetes, compared to non-snorers. Such graded association was also observed amongst the most frequent snorers with higher risk for prediabetes (odds ratio [OR], 1.78; 95% CI, 1.29 to 2.22) and diabetes (OR, 2.03; 95% CI, 1.45 to 2.85). Disruptive snoring (OR, 1.60; 95% CI, 1.12 to 2.28) and near-daily disruptive breathing (OR, 2.18; 95% CI, 1.02 to 4.19) were associated with higher odds for diabetes. Such findings remained robust after additional adjustment for sleep duration, excessive daytime sleepiness, unwakefulness, and sleep-deprived driving.

Conclusion: Snoring is associated with impaired glucose metabolism even in otherwise metabolically healthy adults. Habitual snorers may require lifestyle modifications and pharmacological treatment to improve glycemic profile.

Keywords: Diabetes mellitus, type 2; Prediabetic state; Snoring

INTRODUCTION

A growing body of epidemiological evidence suggests that habitual snoring is an important risk factor for the development and exacerbation of cardiovascular and metabolic complications, including type 2 diabetes mellitus [1-3]. Considering that snoring is the most common and salient symptom of obstructive sleep apnea (OSA) [4], it is consistently associated with both high prevalence and incidence of type 2 diabetes mellitus among otherwise healthy adults [5]. Poor glycemic control amongst snorers prevails, even after accounting for other sleep-related conditions, such as extreme sleep duration, excessive daytime sleepiness, and chronic fatigue [6-11].

Considering that good sleep quality is essential to maintain normal physiological function to regulate normal somatic, cognitive, and psychological processes, it is important to examine the extent which snoring is associated with glycemic maintenance. The recent Korean statistics showed that among

adults 30 years or older, prevalence of prediabetes is 25.3% and 14.4% for type 2 diabetes mellitus; their pervasiveness escalated drastically with older age [12]. Considering that both prediabetes and diabetes populations are at increased risk for microvascular (chronic kidney disease, neuropathies, and retinopathy) and cardiovascular diseases (CVD) [13], early detection and management of glycemic disorder are crucial.

Whether various characteristics of snoring are associated with elevated risk of both prediabetes and type 2 diabetes mellitus is not well-established in the general population. Moreover, previous studies primarily utilized a single marker of sleep-disordered breathing rather than incorporating comprehensive aspects of sleep. Given the poor prognostics of uncontrolled glycemic state in regard to the CVD progression, investigating whether snoring can be indicative of adverse glycemic state may aid in identifying high-risk or already prevalent individuals for prediabetes and diabetes. In this context, the objective of this study is to examine the association of various characteristics of snoring with prediabetes and type 2 diabetes mellitus, independent of other sleep characteristics among community-dwelling Korean adults. We hypothesized that individuals presenting higher severity (louder sound and greater disruptiveness) and frequency of snoring will have positively graded risk for prediabetes and type 2 diabetes mellitus, compared to non-snoring participants.

METHODS

Study population
The Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) Study has been approved by the Institutional Review Boards of Severance Hospital, Yonsei University Health System, Seoul, Korea (4-2013-0661). Written informed consent has been obtained from all participants prior to the baseline survey. Participants were ensured that they can withdraw from the study at any time, regardless of its cause, without any repercussions.

The study participants consisted of healthy community-dwelling capital residents of Republic of Korea, between the age of 30 to 64 years, who were enrolled in the CMERC cohort. Briefly, the CMERC study aimed to identify novel risk factors and to investigate distribution and effects of known cardiac and metabolic diseases risk factors, ultimately to develop improved CVD prediction tools for the general Korean population [14]. Adhering to standardized protocols, trained researchers collected detailed information on socioeconomic status, health behaviors, disease history, nutrition, and psychosocial characteristics and performed blood and urine tests [14]. In the present study, among 4,060 participants who have undergone baseline examination at the CMERC center 1 between 2013 and 2018, participants either currently undergoing cancer treatment, diagnosed with heart failure or angina pectoris, or missing information on glycemic index were excluded, yielding 3,948 participants (1,800 male and 2,548 female) for the final analysis.

Assessment of exposure
A face-to-face interview obtained information on snoring and other sleep-related variables based on the Korean version of the Berlin Questionnaire [15]. Briefly, the Berlin Questionnaire is one of the most widely and readily used screening tools for OSA. In reference to polysomnography results, previous validation studies confirmed its sensitivity of 84.4% and specificity of 35.3% in both general population and sleep clinic patient-based studies [16,17]. Another systematic review confirmed that among sleep clinic patients or self-reported habitual snorers, the Berlin Questionnaire showed substantial OSA predictability, with sensitivity and specificity as high as 81% and 80%, respectively [18,19]. Considering that in-laboratory polysomnography, currently the gold standard tool for OSA diagnosis, is infeasible for large-scale epidemiologic studies, Berlin Questionnaire collects sleep behavior in cost- and time-efficient manner. In this study, participants were inquired whether they are a habitual snorer. If affirmative, they were subsequently asked to rate their snoring frequency: never or rare, seldom (1 to 2 time/month), sometimes (1 to 2 time/week), often (3 to 4 time/week), or frequent (almost every night). The following question on sleep-disordered breathing ("Has anyone noticed that you quit breathing during your sleep?") was evaluated in the same manner. The respondents rated the intensity of their snoring: slightly louder than breathing, as loud as talking, louder than talking, or very loud (can be heard in adjacent rooms). Lastly, participants were inquired whether own snoring has bothered bed partners); the answer was dichotomized to either a "yes" or a "no."

To simultaneously account for other various sleep-related factors, participants were additionally asked to report their weekday/workday sleep duration in exact hours and minutes, subsequently categorized into ≤5, 6, 7, 8, or ≥9 hours. Frequency of unwakefulness (fatigue after waking up), excessive

daytime sleepiness (feeling tired or fatigued during day/active time), and history of sleep-deprived driving were also inquired.

Based on the responses to the aforementioned questions, we identified five sleep variables: snoring (frequency/intensity/disordered breathing/disruptiveness), sleep duration, unwakefulness, excessive daytime sleepiness, and sleep-deprived driving. Our primary analysis focused on various characteristics of snoring, accounting for other aforementioned sleep variables.

Assessment of glycemic profile

Participants underwent blood test after overnight fasting for a minimum of 8 hours. Fasting plasma glucose levels were assessed using colorimetry method (ADIVA1800 Auto Analyzer; Siemens medical Sol., Deerfield, IL, USA) and glycosylated hemoglobin (HbA1c) was analyzed using high-performance liquid chromatograph (Variant II Turbo Hemoglobin Testing System; Bio-Rad, Irvine, CA, USA).

Prediabetes was defined as a fasting glucose level between 100 mg/dL and 125 mg/dL or HbA1c level between 5.7% and 6.4%. Type 2 diabetes mellitus was defined as fasting glucose level ≥126 mg/dL, HbA1c ≥6.5%, a self-reported physician-diagnosis, or current use of oral glucose-lowering drugs or insulin injection. The CMERC study did not collect sufficient information (e.g., C-peptide levels) enough to identify every subtype previously diagnosed; however, the entailed information regarding history of autoimmune or other chronic diseases, thereby able enabled us to distinguish between type 2 diabetes mellitus and other types of diabetes, such as type 1 diabetes mellitus or maturity onset diabetes of the young.

Assessment of covariates

Demographics, health-related behaviors, and disease history were obtained via face-to-face interview. Household income was categorized into cohort-specific quartile. Longest held and current occupation were classified into white or blue collar or unemployed. Education level was categorized into four groups: elementary school or below, middle school, high school, or college/university. Physical activity was assessed by the Korean version of the International Physical Activity Questionnaire standard [20]. The total metabolic equivalent of task was then categorized into quartile. Alcohol consumption and cigarette smoking were divided into non-, previous-, and current drinker/smoker. Information on familial and personal morbidity history included the age at first diagnosis of common chronic diseases, such as hypertension, diabetes mellitus, and so on.

Accordingly, participants presented prescription records entailing previous and current treatment status, including types of oral hypoglycemic medications or insulin injection.

Height was measured to the nearest 0.1 cm using stadiometers (DS-102; Jenix, Seoul, Korea), and weight was measured to the nearest 0.1 kg on a digital scale (DB-150; CAS, Seongnam, Korea). To minimize measurement variability, a zero-point adjustment was routinely conducted using a standard ruler (170 cm) and weights (20, 40, and 60 kg). Body mass index (BMI) was calculated as a ratio of weight in kilograms to height in squared meters. We defined obesity as BMI ≥25 kg/m^2 based on the Asia-Pacific classification from the World Health Organization guideline [21]. Blood pressure (BP) was consecutively measured using both single- and double-arm automated oscillometric device (HEM-7080 and HEM-9000 AI; Omron Health, Matsusaka, Japan) at a single sitting; the mean of second and third measurements was adopted for analysis. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, self-reported physician-diagnosis, or current use of antihypertensive medication.

Statistical analysis

We compared anthropometric, socioeconomic, lifestyle, and morbidity characteristics of the participants across healthy glycemic ("normal"), prediabetes, and type 2 diabetes mellitus groups using one-way analysis of variance. Next, we employed multivariable linear regression model to assess the association between individual dimension of snoring and fasting glucose level and HbA1c concentration, separately. Then, to examine whether snoring and its subcomponents are associated with increased risk of prediabetes and type 2 diabetes mellitus, we employed multivariable multinomial logistic regression to compare associations among normal, prediabetes, and type 2 diabetes mellitus groups. All results are presented in odds ratio (OR) and 95% confidence interval (95% CI).

We selected potential confounders based on a review of the literature and logical assessment of potential causal relationships accounting for biological plausibility. In the first model, we adjusted for age and sex. In the second model, we additionally adjusted for BMI, hypertension prevalence, and socioeconomic status, including education level, household income, and longest held occupation. In the third model, we additionally adjusted for well-known cardiovascular and metabolic behavioral risk factors, including current smoking and drinking status and physical activity. To account for residual confound-

ing even after adjusting for BMI and hypertension prevalence, subgroup analyses were done by further stratifying by obesity and hypertension status. To further explore whether the effect of snoring was independent of other sleep conditions, we simultaneously adjusted for all sleep-related variables, including sleep duration, unwakefulness, excessive daytime sleepiness, and sleep-deprived driving.

Hosmer-Lemeshow goodness of fit for logistic regression ensured appropriateness of the model. All statistical tests were two-sided, and the statistical significance was set at a *P* value <0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among 3,893 participants, 1,224 (31.4%) participants had prediabetes and 355 participants (9.1%) had type 2 diabetes mellitus. Table 1 compares the general characteristics of the study population across normoglycemic, prediabetes, and type 2 diabetes mellitus groups. Compared to normoglycemia group, prediabetes and type 2 diabetes mellitus groups were older and higher proportion of male sex, current smoker, obesity, and hypertension. Furthermore, there were significant differences in education level, household income, and drinking history among the three groups. Participants with type 2 diabetes mellitus had the highest proportion of habitual snorer (76.5%), followed by prediabetes group (73.2%) and lastly, the normal group (59.9%).

Table 2 presents age- and sex-adjusted mean comparison of fasting glucose and HbA1c levels by level of each snoring characteristics. Compared to their non-snoring counterpart, participants who habitually snore had higher fasting glucose (92.5 mg/dL vs. 88.2 mg/dL) and HbA1c (5.7% vs. 5.6%) levels. Both indices were incrementally higher with increasing snoring intensity, frequency, disruptiveness, and disrupted breathing.

Table 3 illustrates results from the multivariable linear regression of individual snoring characteristics with fasting glucose and HbA1c level. For each sleep variable dimension, the estimates are obtained in reference to the lowest categorical level; for instance, the analyses on snoring frequency are in reference to the "never or rare" category. In prediabetes group, higher snoring intensity (β=1.20 mg/dL, *P*=0.001), frequency (β=0.99 mg/dL, *P*=0.008), and bothersome snoring (β=0.96 mg/dL, *P*=0.007) were positively associated with fasting glucose level. Similar direction and magnitude of association were observed

in type 2 diabetes mellitus group. Likewise, regardless of glycemic status, higher intensity, frequency, and disruption were also positively associated with HbA1c levels. Such trend remained robust after stratification by sex (Supplementary Table 1).

Table 4 presents results from the multinomial logistic model comparing the risk for prediabetes and type 2 diabetes mellitus across categories of each snoring dimension. All risk levels are in reference to non-snorers with normal glycemic profile. After adjusting for age, sex, and known risk factors of type 2 diabetes mellitus, participants with the most severe snoring were at 1.81 times higher risk (95% CI, 1.07 to 2.33) for prediabetes and 1.84 times higher risk (95% CI, 1.14 to 2.95) for type 2 diabetes mellitus. Such graded association was also noted across more frequent snoring among participants with prediabetes (OR, 1.79; 95% CI, 1.33 to 2.24) and type 2 diabetes mellitus (OR, 2.05; 95% CI, 1.48 to 2.83). Disruptive snoring was associated with 1.59 times higher risk for type 2 diabetes mellitus (95% CI, 1.10 to 2.25) only. Likewise, positively graded association with more frequent disrupted breathing was observed only for type 2 diabetes mellitus; those reporting near-daily disrupted breathing had 2.2 times higher odds for type 2 diabetes mellitus (95% CI, 1.06 to 4.30), compared to those with complacent breathing. As a supplementary analysis, we examined the association of each sleep variable with prediabetes and type 2 diabetes mellitus (Supplementary Table 2). To integrate comprehensive aspects of sleep, we additionally adjusted for these variables when assessing the odds for prediabetes and type 2 diabetes mellitus (Table 4). Additional adjustments did not reverse the direction nor noticeably diminish the strength of association.

In the first subgroup analysis stratified by obesity status, the association between snoring intensity and frequency with type 2 diabetes mellitus remained significant in participants with BMI less than 25 kg/m^2 (Supplementary Table 3). Non-obese participants reporting the highest intensity snoring had 1.54 times higher odds (95% CI, 0.97 to 2.66) for prediabetes and 1.83 times higher odds (95% CI, 1.24 to 2.43) for type 2 diabetes mellitus, compared to normal weight, non-snorers. Moreover, regardless of obesity status, participants reporting higher frequency snoring were at incrementally higher risk for both prediabetes and type 2 diabetes mellitus. The second subgroup analysis stratified participants by hypertension prevalence (Supplementary Table 4). Similarly, participants without hypertension were at higher risk for prediabetes and type 2 diabetes mellitus across more intense and frequent categories of

Table 1. General characteristics of the study population ($n=3,948$)

Variable	Normal ($n=2,369$)	Prediabetes ($n=1,224$)	Diabetes ($n=355$)	P value
Age, yr	49.0±9.8	54.0±7.7	55.4±7.0	<0.001
MET-min/wk	2,747.5±3,619.2	2,888.9±3,702.7	2,769.7±3,229.7	0.531
Fasting glucose, mg/dL	84.8±6.8	94.3±10.1	129.3±41.0	<0.001
HbA1c, %	5.3±0.2	5.9±0.2	7.2±1.3	<0.001
Sex				<0.001
Male	797 (33.6)	432 (35.3)	171 (48.2)	
Female	1,572 (66.4)	792 (64.7)	184 (51.8)	
Education level				<0.001
Elementary school	98 (4.1)	87 (7.1)	36 (10.1)	
Middle school	164 (6.9)	124 (10.1)	52 (14.7)	
High school	871 (36.8)	517 (42.2)	146 (41.1)	
College/University	1,235 (52.2)	496 (40.5)	121 (34.1)	
Household income				0.020
Low	579 (24.4)	276 (22.6)	111 (31.3)	
Middle-low	572 (24.2)	315 (25.7)	75 (21.1)	
Middle-high	574 (24.2)	297 (24.3)	92 (25.9)	
High	644 (27.2)	336 (27.5)	77 (21.7)	
Occupation				0.012
White collar	951 (40.1)	404 (33.0)	125 (35.2)	
Blue collar	650 (27.4)	399 (32.6)	122 (34.4)	
Unemployed	768 (32.4)	421 (34.4)	108 (30.4)	
Cigarette smoking				<0.001
Non-smoker	1,651 (70.0)	844(69.0)	198 (55.8)	
Former smoker	385 (16.3)	229 (18.7)	86 (24.2)	
Current smoker	333 (14.1)	151 (12.3)	71 (20.0)	
Alcohol consumption				0.020
Non-drinker	489 (20.6)	308 (25.2)	77 (21.7)	
Former drinker	105 (4.4)	44 (3.6)	24 (6.8)	
Current drinker	1,775 (74.9)	872 (71.2)	254 (71.6)	
Obese, BMI ≥25 kg/m²				<0.001
No	1,741 (73.5)	724 (59.2)	150 (42.3)	
Yes	628 (26.5)	500 (40.9)	205 (57.8)	
Hypertension				<0.001
No	1,911 (80.7)	837 (68.4)	183 (51.6)	
Yes	458 (19.3)	387 (31.6)	172 (48.5)	
Habitual snoring				<0.001
No	1,020 (43.1)	371 (30.3)	86 (24.2)	
Yes	1,349 (56.9)	853 (69.7)	269 (75.8)	

Values are presented as mean±standard deviation or number (%). *P* value was derived from the one-way variance of analysis (ANOVA) for multiple comparisons.

MET, metabolic equivalent of task; HbA1c, glycosylated hemoglobin; BMI, body mass index.

Table 2. The mean level of fasting glucose and HbA1c by characteristics of snoring ($n = 3,948$)

Snoring characteristic	Participants	Fasting glucose, mg/dL	P value	HbA1c, %	P value
Presence			<0.001		<0.001
No	1,477 (37.4)	88.2±12.0		5.6±0.6	
Yes	2,471 (62.6)	92.5±15.9		5.7±0.7	
Intensity			<0.001		<0.001
Does not snore	1,477 (37.4)	88.2±12.0		5.6±0.6	
Slightly louder than breathing	1,091 (27.8)	90.7±14.4		5.7±0.7	
As loud as talking	766 (19.5)	93.7±17.1		5.8±0.8	
Louder than talking	376 (9.6)	94.0±15.9		5.7±0.6	
Very loud.	216 (5.5)	94.6±17.6		5.8±0.9	
Frequency			<0.001		<0.001
Never or nearly never	1,582 (40.3)	90.9±14.5		5.6±0.5	
1–2 times a month	552 (14.1)	90.8±14.3		5.7±0.8	
1–2 times a week	762 (19.4)	92.2±15.7		5.7±0.8	
3–4 times a week	495 (12.6)	92.4±15.6		5.7±0.7	
Nearly every day	534 (13.6)	95.0±17.9		5.8±0.7	
Disruptive to others			<0.001		<0.001
Does not snore	1,477 (37.4)	88.2±12.0		5.6±0.6	
No	1,806 (46.0)	92.2±15.8		5.7±0.7	
Yes	644 (16.4)	93.4±16.1		5.7±0.7	
Disrupted breathing			<0.001		<0.001
Never or nearly never	3,690 (90.7)	91.1±18.4		5.6±0.7	
1–2 times a month	110 (2.8)	95.7±18.8		5.8±0.7	
1–2 times a week	124 (3.1)	98.8±23.3		5.8±0.9	
3–4 times a week	71 (1.8)	99.1±33.9		5.9±1.0	
Nearly every day	63 (1.6)	99.8±25.5		6.1±1.1	

Values are presented as number (%) or mean±standard deviation. *P* value was derived from the one-way variance of analysis (ANOVA) for multiple comparisons.
HbA1c, glycosylated hemoglobin.

snoring, but the experience of bothersome snoring nor disrupted breathing did not yield any significant results.

DISCUSSION

In this community-dwelling cohort of middle-aged Korean adults, snoring frequency and intensity were significantly associated with higher odds for both prediabetes and type 2 diabetes mellitus, independent of socioeconomic, behavioral, and other sleep-related factors. Furthermore, snoring also showed continuous association with elevated glycemic biomarkers in among persons with type 2 diabetes mellitus. Therefore, in a primary prevention setting, persons experiencing habitual

snoring or OSA may be at high-risk for current or future type 2 diabetes mellitus, and timely screening for diabetes may be advisable in these individuals. Conversely, in patients already with type 2 diabetes mellitus, habitual snorers may be potential targets for lifestyle modifications or more aggressive clinical interventions to improve sleep quality and to optimize glycemic control.

Our findings on the association between snoring and type 2 diabetes mellitus are consistent with previous studies. Among large Chinese community studies, both occasional and habitual snoring were significantly associated 1.4 times higher risk for impaired fasting glucose and 1.1 times higher risk for impaired glucose tolerance, even after adjusting for diabetes- and

Table 3. Association of individual characteristics of snoring with fasting glucose and HbA1c ($n=3,948$)

Snoring characteristic	Model 1		Model 2		Model 3	
	β	P value	β	P value	β	P value
Fasting glucose, mg/dL						
Normal glycemic profile						
Intensity	1.24	0.008	1.21	0.009	1.20	0.009
Frequency	1.03	0.027	1.04	0.027	1.02	0.028
Bothersome	0.71	0.001	0.66	0.004	0.63	0.009
Disrupted breathing	0.34	0.132	0.32	0.173	0.32	0.173
Prediabetes						
Intensity	1.26	0.001	1.19	0.001	1.20	0.001
Frequency	1.03	<0.001	1.02	<0.001	0.99	0.008
Bothersome	1.00	0.001	0.97	0.007	0.96	0.007
Disrupted breathing	0.55	0.056	0.50	0.144	0.49	0.168
Type 2 diabetes mellitus						
Intensity	1.04	<0.001	1.00	<0.001	0.93	0.016
Frequency	1.09	<0.001	1.03	0.012	0.97	0.018
Bothersome	1.04	0.019	1.02	0.025	1.00	0.027
Disrupted breathing	0.58	0.200	0.57	0.221	0.56	0.241
HbA1c, %						
Normal glycemic profile						
Intensity	0.03	0.008	0.03	0.007	0.03	0.007
Frequency	0.03	<0.001	0.02	<0.001	0.02	<0.001
Bothersome	0.04	<0.001	0.03	0.009	0.03	0.009
Disrupted breathing	0.02	0.008	0.01	0.157	0.01	0.148
Prediabetes						
Intensity	0.04	<0.001	0.04	<0.001	0.04	<0.001
Frequency	0.04	<0.001	0.04	<0.001	0.04	<0.001
Bothersome	0.06	<0.001	0.06	<0.001	0.05	0.004
Disrupted breathing	0.04	<0.001	0.04	<0.001	0.04	<0.001
Type 2 diabetes mellitus						
Intensity	0.02	0.009	0.02	0.008	0.02	0.008
Frequency	0.03	<0.001	0.02	0.004	0.02	0.006
Bothersome	0.008	0.040	0.006	0.114	0.006	0.118
Disrupted breathing	0.002	0.413	0.001	0.621	0.001	0.602

The estimates are in reference to the lowest ordinal category of each snoring characteristics. Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, body mass index, hypertension prevalence, education level, household income, and occupation. Model 3 is adjusted for age, sex, body mass index, hypertension prevalence, education level, household income, occupation, cigarette smoking, alcohol consumption, and physical activity.

HbA1c, glycosylated hemoglobin.

sleep-related covariates [13]. The Cardiovascular Health Study also demonstrated that diverse symptoms of OSA, including daytime sleepiness and disruptive snoring, were associated with elevated fasting glucose level and lower insulin sensitivity [22]. In the Nurses' Health Study, the multivariable-adjusted hazard ratio of developing type 2 diabetes mellitus was 1.41

Table 4. Association of individual characteristics of snoring with prediabetes and type 2 diabetes mellitus ($n=3,948$)

Snoring characteristic	Prediabetes				Type 2 diabetes mellitus			
	No. of case (%)	OR (95% CI)			No. of case (%)	OR (95% CI)		
		Model 1	Model 2	Model 3		Model 1	Model 2	Model 3
Intensity								
Does not snore	371 (30.4)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	86 (24.4)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Slightly louder than breathing	361 (29.6)	1.32 (1.11–1.54)	1.27 (1.07–1.60)	1.32 (1.08–1.61)	92 (26.1)	1.36 (1.02–1.88)	1.40 (1.05–1.82)	1.44 (1.03–1.82)
As loud as talking	269 (22.0)	1.54 (1.24–1.96)	1.41 (1.19–1.88)	1.47 (1.21–1.97)	98 (27.8)	2.10 (1.50–2.92)	1.70 (1.21–2.39)	1.71 (1.21–2.38)
Louder than talking	140 (11.5)	1.66 (1.33–2.03)	1.50 (1.17–1.96)	1.52 (1.11–2.00)	42 (11.9)	2.16 (1.56–3.24)	1.80 (1.15–1.97)	1.80 (1.15–1.96)
Very loud	80 (6.6)	2.01 (1.40–2.44)	1.84 (1.09–2.29)	1.81 (1.07–2.33)	34 (9.7)	2.62 (1.66–4.10)	2.24 (1.84–2.95)	1.84 (1.14–2.95)
Frequency								
Never or nearly never	410 (33.6)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	90 (25.6)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1–2 times a month	172 (14.1)	1.40 (1.04–1.89)	1.36 (1.02–1.87)	1.33 (1.00–1.79)	46 (13.1)	1.45 (1.10–1.96)	1.45 (1.03–1.99)	1.46 (1.04–1.99)
1–2 times a week	251 (20.6)	1.50 (1.08–1.91)	1.44 (1.02–1.85)	1.47 (1.05–1.87)	78 (22.2)	1.71 (1.21–2.36)	1.51 (1.07–2.13)	1.50 (1.05–2.13)
3–4 times a week	185 (15.2)	1.62 (1.09–2.01)	1.57 (1.05–1.97)	1.57 (1.07–1.95)	55 (15.6)	1.90 (1.31–2.75)	1.58 (1.07–2.31)	1.60 (1.13–2.31)
Nearly every day	202 (16.6)	1.83 (1.30–2.33)	1.78 (1.29–2.22)	1.79 (1.33–2.24)	83 (23.6)	2.72 (1.94–3.82)	2.03 (1.45–2.85)	2.05 (1.48–2.83)
Disruptiveness								
Does not snore	371 (30.4)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	86 (24.4)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Not disruptive	624 (51.1)	1.35 (1.06–1.66)	1.26 (0.99–1.57)	1.29 (1.01–1.60)	185 (52.6)	1.70 (1.26–2.20)	1.43 (1.07–1.90)	1.38 (1.01–1.88)
Disruptive	226 (18.5)	1.47 (1.12–1.80)	1.13 (0.83–1.50)	1.16 (0.87–1.59)	81 (23.0)	2.05 (1.44–2.85)	1.60 (1.12–2.28)	1.59 (1.10–2.25)
Disrupted breathing								
Never or nearly never	1,105 (90.3)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	288 (81.1)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
1–2 times a month	29 (2.4)	0.65 (0.30–1.23)	0.73 (0.41–1.40)	0.78 (0.45–1.50)	18 (5.1)	1.79 (1.07–3.10)	1.68 (1.02–2.95)	1.66 (0.91–2.92)
1–2 times a week	39 (3.2)	1.67 (1.11–2.67)	1.51 (0.90–2.39)	1.53 (0.88–2.19)	23 (6.5)	2.09 (1.25–3.50)	1.83 (1.05–3.08)	1.83 (1.05–3.07)
3–4 times a week	24 (2.0)	2.13 (1.26–3.52)	1.88 (0.69–2.46)	1.87 (0.69–2.43)	14 (3.9)	2.20 (1.17–4.20)	1.90 (1.07–3.65)	1.90 (1.07–3.65)
Nearly every day	27 (2.2)	2.54 (1.32–4.88)	1.27 (0.63–2.07)	1.28 (0.64–2.09)	12 (3.4)	2.76 (1.40–5.13)	2.18 (1.02–4.19)	2.20 (1.06–4.30)

The estimates are derived from the multivariable multinomial logistic regression. The estimates are in reference to the normal glycemic group (participants without prediabetes and type 2 diabetes mellitus). Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, body mass index, hypertension prevalence, education level, household income, occupation, cigarette smoking, alcohol consumption, and physical activity. Model 3 is age, sex, body mass index, hypertension prevalence, education level, household income, occupation, cigarette smoking, alcohol consumption, physical activity, sleep duration, unwakefulness, excessive daytime sleepiness, and sleep-deprived driving.

OR, odds ratio; CI, confidence interval.

(95% CI, 1.22 to 1.63) for self-reported occasional snorers and 2.03 (95% CI, 1.71 to 2.40) for habitual snorers [5,23]. In a Korean study, compared to non-snorers, habitual snorers showed analogous baseline fasting glucose and insulin levels, but later underwent more drastic increase over 1- and 2-hour oral glucose tolerance test [24]. In another community-dwelling Korean population, the homeostatic model assessment-insulin resistance showed dose-response relationship across higher frequency snoring gradient in female [25].

However, our study extends the previous findings in two important ways. Firstly, it examined multiple characteristics of snoring, rather than simply assessing its absence or presence. Secondly, it examined both stages of diabetes (prediabetes and type 2 diabetes mellitus), simultaneously adjusting for surrogate markers for sleep fragmentation, obstruction, recurrent arousals, etc.

The observed association between snoring and type 2 diabetes mellitus is biologically plausible. Snoring is a form of abnormal breathing during sleep that inhibits good quality sleep via oxygen desaturation and upper airway obstruction [11]. This, resultant intermittent hypoxia leads to insulin resistance and disrupts glucose metabolism via several pathways. First, increased sleep fragmentation and frequent arousals trigger pro-inflammatory cascade by elevating interleukin-6, C-reactive protein, and fibrinogen levels and lowering albumin levels, thereby systematically damaging glucose stability and beta-cell function [26]. Another proposed mechanism is that snoring activates sympathetic nervous system, resulting in catecholamine elevation and hypothalamic-pituitary-adrenal axis activation. This conjointment of elevated cortisol, formation of reactive oxygen species, and increased oxidative stress alter sleep, thereby glucose metabolism [27-30]. Lastly, snoring may be manifestation of behavioral risk factors of type 2 diabetes mellitus, such as lack of physical activity. Physical inactivity is known to reciprocate circulating leptin and ghrelin levels that are responsible for increased appetite, thereby encourage higher caloric intake [31]. Excessive energy consumption coupled with reduced physical activity can disrupt food intake pattern and energy expenditure, accelerating obesity development and glycemic deterioration [31].

Despite numerous proposed mechanisms, other studies have shown divergent findings on the association between snoring and prevalence or manifestation of type 2 diabetes mellitus. Several studies demonstrated that daytime sleepiness [1,9,32] or short sleep duration [33,34] was rather associated with al-

tered glucose metabolism, poor glycemic control, and insulin resistance. Perhaps, regardless of sleep phenotype, considering the high prevalence of snoring in the elderly population, OSA symptoms may be benign part of the typical aging process without reflecting a specific glycemic or metabolic pathology. In endocrinological context, sex-specific steroid hormones and dimorphism may support female-specific associations reported in previous research [35,36]. Varied data collection tools and variable treatment also contribute to discrepancies in effect size. Foremost, the presence of obesity and hypertension yield synergistic effect on diabetes. The amalgamation of adiposity and sleep breathing disturbances embodies high-risk for type 2 diabetes mellitus and CVD [37]. Therefore, considering the high likelihood that adjustments may still leave residual confounding, we performed subgroup analyses, in which we confirmed that the association persisted even in non-obese and normotensive groups.

Strengths of the present study include meticulous breakdown of snoring and comparison of associations between its individual dimension with prediabetes and type 2 diabetes mellitus risk. Moreover, the infrastructure of this large, general population cohort study adeptly served in ascertaining both the exposure and outcome variables in standardized manners. Finally, the nature of healthy community-based cohort allows to generalize our findings in detecting high-risk group for prediabetes/type 2 diabetes mellitus in ubiquitous clinic settings.

Several limitations merit consideration when interpreting our findings. Due to the cross-sectional study design, we were unable to infer specific directionality of the association between snoring and type 2 diabetes mellitus. Assessment of snoring and other sleep variables might have resulted in non-differential misclassification bias, due to differing recall capability and awareness of own sleep habits by the presence of bed partners. While subjective, use of sleep questionnaires still have fair clinical applicability for its low cost and time efficiency. Moreover, previous studies have reported that self-reported snoring correlates well with objective measures, especially among frequent snorers [38]. Availability of diverse sleep collection methodology warrants further studies, in which self-reported sleep measures be replaced with wearable actigraphy or selectively recruit high-risk individuals to undergo polysomnography to confirm reliability of sleep questionnaires. Furthermore, prior studies have shown that individuals who are unmarried or without bed partners tend to underreport their snoring [39]. Restricting the participants to those with bed partners may in-

crease the accuracy of sleep measurements.

In summary, increasing snoring frequency and intensity were independently associated with risk of both prediabetes and type 2 diabetes mellitus in middle-aged adults. The associations persisted after adjustment for and stratification by obesity, hypertension, and other sleep variables. Snoring may impair glucose metabolism even in otherwise metabolically health adults; in the light of these findings, screening for type 2 diabetes mellitus may be warranted in asymptomatic individuals with habitual snoring. Furthermore, snoring may be a risk factor for poor glycemic control in diabetes, thereby warrants close and periodic surveillance and potential lifestyle and pharmacological interventions.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2019.0128.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: S.M.J.C., J.S.S., H.C.K.
Acquisition, analysis, or interpretation of data: S.M.J.C., H.L., H.C.K.
Drafting the work or revising: S.M.J.C., H.L., H.C.K.
Final approval of the manuscript: S.M.J.C., H.L., J.S.S., H.C.K.

ORCID

So Mi Jemma Cho *https://orcid.org/0000-0003-2460-3335*
Hyeon Chang Kim *https://orcid.org/0000-0001-7867-1240*

ACKNOWLEDGMENTS

REFERENCES

1. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res 2004;56:497-502.
2. Hu FB, Willett WC, Manson JE, Colditz GA, Rimm EB, Speizer FE, Hennekens CH, Stampfer MJ. Snoring and risk of cardiovascular disease in women. J Am Coll Cardiol 2000;35:308-13.
3. Lee SA, Amis TC, Byth K, Larcos G, Kairaitis K, Robinson TD, Wheatley JR. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep 2008;31:1207-13.
4. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. Proc Am Thorac Soc 2008;5:207-17.
5. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. Am J Epidemiol 2002;155:387-93.
6. Li D, Liu D, Wang X, He D. Self-reported habitual snoring and risk of cardiovascular disease and all-cause mortality. Atherosclerosis 2014;235:189-95.
7. Li Y, Gao X, Winkelman JW, Cespedes EM, Jackson CL, Walters AS, Schernhammer E, Redline S, Hu FB. Association between sleeping difficulty and type 2 diabetes in women. Diabetologia 2016;59:719-27.
8. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. Diabetes Care 2006;29:657-61.
9. Lindberg E, Berne C, Franklin KA, Svensson M, Janson C. Snoring and daytime sleepiness as risk factors for hypertension and diabetes in women: a population-based study. Respir Med

2007;101:1283-90.

10. Tuomilehto H, Peltonen M, Partinen M, Lavigne G, Eriksson JG, Herder C, Aunola S, Keinänen-Kiukaanniemi S, Ilanne-Parikka P, Uusitupa M, Tuomilehto J, Lindstrom J; Finnish Diabetes Prevention Study Group. Sleep duration, lifestyle intervention, and incidence of type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study. Diabetes Care 2009;32:1965-71.

11. Zhang SX, Khalyfa A, Wang Y, Carreras A, Hakim F, Neel BA, Brady MJ, Qiao Z, Hirotsu C, Gozal D. Sleep fragmentation promotes NADPH oxidase 2-mediated adipose tissue inflammation leading to insulin resistance in mice. Int J Obes (Lond) 2014;38:619-24.

12. Kim BY, Won JC, Lee JH, Kim HS, Park JH, Ha KH, Won KC, Kim DJ, Park KS. Diabetes fact sheets in Korea, 2018: an appraisal of current status. Diabetes Metab J 2019;43:487-94.

13. Wang HB, Yan WH, Dou JT, Lu ZH, Wang BA, Mu YM. Association between self-reported snoring and prediabetes among adults aged 40 years and older without diabetes. Chin Med J (Engl) 2017;130:791-7.

14. Shim JS, Song BM, Lee JH, Lee SW, Park JH, Choi DP, Lee MH, Ha KH, Kim DJ, Park S, Lee WW, Youm Y, Shin EC, Kim HC. Cohort profile: the cardiovascular and metabolic diseases etiology research center cohort in Korea. Yonsei Med J 2019;60:804-10.

15. Kang K, Park KS, Kim JE, Kim SW, Kim YT, Kim JS, Lee HW. Usefulness of the Berlin questionnaire to identify patients at high risk for obstructive sleep apnea: a population-based door-to-door study. Sleep Breath 2013;17:803-10.

16. Jeon HJ, Bang YR, Yoon IY. A validation study on three screening questionnaires for obstructive sleep apnea in a Korean community sample. Sleep Breath 2019;23:969-77.

17. Kim B, Lee EM, Chung YS, Kim WS, Lee SA. The utility of three screening questionnaires for obstructive sleep apnea in a sleep clinic setting. Yonsei Med J 2015;56:684-90.

18. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. Anesthesiology 2008;108:822-30.

19. Lam B, Lam DC, Ip MS. Obstructive sleep apnoea in Asia. Int J Tuberc Lung Dis 2007;11:2-11.

20. Oh JY, Yang YJ, Kim BS, Kang JH. Validity and reliability of Korean Version of International Physical Activity Questionnaire (IPAQ) short form. J Korean Acad Fam Med 2007;28:532-41.

21. World Health Organization, International Obesity Task Force. The Asian-Pacific perspective: redefining obesity and its treatment. Geneva: WHO Western Pacific Region, 2000.

22. Strand LB, Carnethon M, Biggs ML, Djousse L, Kaplan RC, Siscovick DS, Robbins JA, Redline S, Patel SR, Janszky I, Mukamal KJ. Sleep disturbances and glucose metabolism in older adults: the cardiovascular health study. Diabetes Care 2015;38:2050-8.

23. Renko AK, Hiltunen L, Laakso M, Rajala U, Keinanen-Kiukaanniemi S. The relationship of glucose tolerance to sleep disorders and daytime sleepiness. Diabetes Res Clin Pract 2005; 67:84-91.

24. Joo S, Lee S, Choi HA, Kim J, Kim E, Kimm K, Kim J, Shin C. Habitual snoring is associated with elevated hemoglobin A1c levels in non-obese middle-aged adults. J Sleep Res 2006;15: 437-44.

25. Lee YH, Kweon SS, Choi JS, Nam HS, Park KS, Choi SW, Oh SH, Kim SA, Shin MH. A gender-specific association between self-reported snoring and hemoglobin A1c levels in a general population without type 2 diabetes mellitus. Yonsei Med J 2017;58:1152-9.

26. Alam I, Lewis K, Stephens JW, Baxter JN. Obesity, metabolic syndrome and sleep apnoea: all pro-inflammatory states. Obes Rev 2007;8:119-27.

27. Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J. Nocturnal cortisol release in relation to sleep structure. Sleep 1992;15:21-7.

28. Bloch-Damti A, Bashan N. Proposed mechanisms for the induction of insulin resistance by oxidative stress. Antioxid Redox Signal 2005;7:1553-67.

29. Alberti A, Sarchielli P, Gallinella E, Floridi A, Floridi A, Mazzotta G, Gallai V. Plasma cytokine levels in patients with obstructive sleep apnea syndrome: a preliminary study. J Sleep Res 2003;12:305-11.

30. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia 2000;43:533-49.

31. Song Q, Liu X, Zhou W, Wang X, Wu S. Short-term changes in sleep duration and risk of type 2 diabetes: Kailuan prospective study. Medicine (Baltimore) 2016;95:e5363.

32. Empana JP, Dauvilliers Y, Dartigues JF, Ritchie K, Gariepy J, Jouven X, Tzourio C, Amouyel P, Besset A, Ducimetiere P. Excessive daytime sleepiness is an independent risk indicator for cardiovascular mortality in community-dwelling elderly: the three city study. Stroke 2009;40:1219-24.

33. Knutson KL, Ryden AM, Mander BA, Van Cauter E. Role of sleep duration and quality in the risk and severity of type 2 dia-

betes mellitus. Arch Intern Med 2006;166:1768-74.

34. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, Redline S. Sleep duration and biomarkers of inflammation. Sleep 2009;32:200-4.

35. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2003;167:1181-5.

36. Fietze I, Laharnar N, Obst A, Ewert R, Felix SB, Garcia C, Glaser S, Glos M, Schmidt CO, Stubbe B, Volzke H, Zimmermann S, Penzel T. Prevalence and association analysis of obstructive sleep apnea with gender and age differences: results of SHIP-Trend. J Sleep Res 2019;28:e12770.

37. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G. The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male population. J Intern Med 2000;248:13-20.

38. Bliwise DL, Nekich JC, Dement WC. Relative validity of self-reported snoring as a symptom of sleep apnea in a sleep clinic population. Chest 1991;99:600-8.

39. Kump K, Whalen C, Tishler PV, Browner I, Ferrette V, Strohl KP, Rosenberg C, Redline S. Assessment of the validity and utility of a sleep-symptom questionnaire. Am J Respir Crit Care Med 1994;150:735-41.