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A Gender-Specific Association between Self-Reported Snoring and Hemoglobin A1c Levels in a General Population without Type 2 Diabetes Mellitus

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Purpose: We explored whether a gender difference was evident in terms of the associations of snoring with hemoglobin A1c (HbA1c) and homeostatic model assessment-insulin resistance (HOMA-IR) levels in a healthy population without type 2 diabetes mellitus (DM).

Materials and Methods: We analyzed 2706 males and 4080 females who participated in the baseline survey of the Namwon Study. In terms of self-reported snoring frequency, participants were classified as non-snorers or occasional (1–3 days/week), frequent (4–6 days/week), or constant (7 days/week) snorers. Participants with DM, defined as a fasting blood glucose level ≥126 mg/dL and/or use of insulin or hypoglycemic medication, were excluded from the analysis.

Results: In females, the fully adjusted mean (95% confidence interval) HbA1c levels in non-snorers and in occasional, frequent, and constant snorers were 5.53% (5.47–5.59%), 5.53% (5.47–5.59%), 5.57% (5.49–5.64%), and 5.57% (5.51–5.64%), respectively, reflecting a dose-response relationship (p trend=0.004). Compared with female non-snorers, the risk of an elevated HbA1c level (top quintile, ≥5.9%) in constant snorers remained significant (odds ratio 1.30, 95% confidence interval 1.02–1.66) after full adjustment. In addition, in females, a significant linear trend in HbA1c level odds ratio by increased snoring frequency was apparent (p trend=0.019 in model 3). In contrast, no significant association between snoring frequency and HbA1c level was identified in males. No significant association between snoring frequency and HOMA-IR was detected in either gender.

Conclusion: We discovered a gender-specific association between snoring and HbA1c level in a healthy, community-dwelling population free of DM.

Key Words: Snoring, hemoglobin A, glycosylated, insulin resistance, gender

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INTRODUCTION

Snoring, an indicator of increased airway resistance, is commonly regarded as a surrogate marker of obstructive sleep apnea.[1] Earlier epidemiological studies have shown that snoring is associated with metabolic syndrome, hypertension, and diabetes mellitus (DM).[2-4] Moreover, recent studies have indicated that habitual snoring is a significant risk factor for cardiovascular disease.[5,6] Both metabolic pathways and non-metabolic features such as subclinical atherosclerosis may mediate the association between snoring and cardiovascular disease.[7,8]

Measurement of hemoglobin A1c (HbA1c) is diagnostically valuable when monitoring long-term glycemic control of DM patients. Higher concentrations of HbA1c in such patients, indicating suboptimal control of blood glucose levels over the prior 2–3 months, have been directly linked to long-term diabetic complications such as cardiovascular events and death.[9,10] In addition, recent epidemiological studies have shown that elevated HbA1c concentrations are associated with atherosclerosis and cardiovascular disease, even in individuals without DM.[11-13]

To date, any association between snoring and HbA1c levels in individuals without DM has received little attention. Polysomnography, the gold standard for diagnosis of obstructive sleep apnea, is expensive, labor-intensive, and time-consuming.[14] However, it is important to determine whether snoring, a useful public health screening tool, is significantly associated with HbA1c levels in general populations. Furthermore, although a recent meta-analysis found that habitual snoring was a risk factor for DM only in females,[15] limited information is available on the gender-specific relationship between snoring and HbA1c levels in individuals without DM. Thus, the aim of the present study was to investigate a possible gender difference between self-reported snoring status and HbA1c levels in a community-dwelling general population without DM. This study also evaluated the relationship between snoring frequency and homeostatic model assessment-insulin resistance (HOMA-IR), a widely utilized method of quantifying insulin resistance.

MATERIALS AND METHODS

Study population

The study population consisted of both males and females who participated in the baseline survey of the Namwon Study between 2004 and 2007.[16] Of the total of 10667 individuals enrolled, 10076 aged ≥50 years were initially included. Next, 2058 participants for whom information on snoring was lacking (totals of 1956 who were not surveyed in terms of snoring in 2004 and 102 who were inadequately surveyed in 2005–2007), and 204 participants for whom no information on HbA1c, fasting blood glucose (FBG), and insulin levels was available were excluded. An additional 1028 participants with DM, defined as those using anti-diabetic medications or having a FBG level ≥126 mg/dL, were also excluded. Thus, 6786 participants (2706 males and 4080 females) were included in the final analysis. The study protocol was approved by the Institutional Review Board of Chonnam National University Hospital (I-2007-07-062). All participants were fully informed of the nature of the study, and all provided written informed consent for use of their data.

Interview

Information on demographics, cigarette smoking, alcohol consumption, medical history, and medications used (to treat DM, hypertension, and/or dyslipidemia) was collected using a standardized questionnaire administered by well-trained interviewers. Smoking status was classified into current smoker and current non-smoker. Alcohol consumption was scored as drinks/day. Educational level was scored as elementary school or lower (≤6 years), middle or high school (7–12 years), and college or higher (≥13 years).

Snoring status was assessed in a structured interview that included the two questions: 1) "Do you know or have you ever been told that you snore?" (yes or no) and 2) "How often do you snore?" Snoring frequency was scored as non-snorer, occasional snorer (1–3 days/week), frequent snorer (4–6 days/week), and constant snorer (7 days/week).

Anthropometric and biochemical parameters

Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg with each participant lightly dressed. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured to the nearest 0.1 cm, during expiration, at the midpoint between the lowest rib margin and the iliac crest. Blood pressure was measured on the right upper arm using a mercury sphygmomanometer (Baumanometer; WA Baum Co., Inc., Copiague, NY, USA) fitted with customized cuffs. Three consecutive blood-pressure measurements, performed at 1-min intervals, were taken after each participant had sat for at least 5-min, and the average values were used in the analysis.

Blood was drawn from the antecubital vein in the morning after a 12-h overnight fast; serum was separated on-site and stored at -70°C prior to analysis. Total cholesterol, high-density-lipoprotein (HDL) cholesterol, triglyceride, and FBG levels were analyzed enzymatically using an automatic analyzer (Hitachi-7600; Hitachi Ltd., Tokyo, Japan). HbA1c concentrations were measured by high-performance liquid chromatography (VARIANT II system; Bio-Rad, Hercules, CA, USA). Insulin levels were measured using an automated, chemiluminescent microparticle immunoassay (AxSYM; Abbott Diagnostics, Abbott Park, IL, USA). HOMA-IR was calculated using the formula [FBG (mg/dL)×fasting insulin (μU/mL)/405]. DM was considered present when the FBG level was ≥126 mg/dL or the participant used insulin or hypoglycemic medication (again, participants with DM were excluded from the analysis).

Statistical analysis

We analyzed male and female data separately. Continuous variables are expressed as means±standard deviations and categorical variables as frequencies (with percentages). Differences in characteristics by snoring status were compared using analysis of variance for continuous variables and the chi-squared test for categorical variables. The mean HbA1c concentrations by snoring frequency were compared using a general linear model. Multiple logistic regression was used to evaluate the association between snoring and HbA1c level. All HbA1c concentrations were dichotomized as normal or elevated (highest quintile, ≥5.9%). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for elevation of HbA1c levels by snoring frequency were compared. General linear modeling and logistic regression were sequentially performed as follows: age-adjusted (model 1); further adjusted for educational level, systolic blood pressure, the total-to-HDL cholesterol ratio, triglyceride level, current smoking, alcohol consumption, use of medication to treat hypertension, and use of medication to treat dyslipidemia (model 2); and further adjusted for BMI and WC (model 3). We, thus, sought to identify an independent association between snoring and HbA1c level after excluding the influence of all other glycemic indices. All statistical analyses were performed with the aid of SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of the study population

The characteristics of males and females, by snoring status, are shown in Tables 1 and 2. The mean age of male participants was 64.4±7.0 years and that of females 63.2±7.1 years. The proportions of non-snorers and occasional, frequent, and constant snorers were 46.4, 28.2, 7.7, and 17.7% among males and 48.2, 29.1, 6.4, and 16.3% among females, respectively. The gender difference in the snoring frequency proportion was of borderline significance (p=0.054). In males, FBG, insulin, and HOMA-IR levels exhibited significant linear trends by snoring status, while HbA1c levels did not. However, HbA1c, FBG, insulin, and HOMA-IR levels exhibited significant linear trends by snoring status in females. In either gender, BMI, WC, and alcohol consumption all increased significantly with increasingly severe snoring status (p trend <0.05). Snoring frequency was significantly associated with FBG, insulin, and HOMA-IR in both genders, but was associated with HbA1c in females only (Table 3).

HbA1c and HOMA-IR concentrations by snoring frequency

The gender-specific HbA1c and HOMA-IR concentrations by snoring frequency are presented in Table 4. No significant difference in HbA1c levels between non-snorers and occasional, frequent, and constant snorers was observed when models 1, 2, and 3 were applied to males. In contrast, among females, HbA1c concentrations in frequent and constant snorers were significantly higher than those of non-snorers in models 1 and

Table 1. Characteristics of the Male Study Population by Self-Reported Snoring Frequency (n=2706)

	Non-snorers (n=1256)	Occasional snorers (n=762)	Frequent snorers (n=209)	Constant snorers (n=479)	*p* trend
Age (yr)	65.4±7.0	63.3±6.9	63.3±7.0	63.8±6.9	<0.001
BMI (kg/m²)	23.1±2.7	23.9±2.7	24.2±2.8	24.5±2.8	<0.001
WC (cm)	83.3±7.8	84.8±7.7	85.5±7.5	85.9±8.0	<0.001
Systolic blood pressure (mm Hg)	126.2±17.7	126.2±16.4	127.4±15.9	127.0±18.4	0.239
Diastolic blood pressure (mm Hg)	80.1±10.0	80.8±9.9	81.1±8.9	80.5±10.1	0.440
HbA1c (%)	5.5±0.4	5.5±0.4	5.4±0.4	5.5±0.4	0.766
FBG (mg/dL)	100.2±9.8	101.9±11.0	102.0±11.6	101.5±10.0	0.033
Insulin (μU/mL)	4.3±3.2	4.7±3.9	4.9±4.2	5.0±4.2	0.001
HOMA-IR	1.1±0.9	1.2±1.1	1.2±1.1	1.3±1.1	0.001
Total cholesterol (mg/dL)	178.1±34.2	181.8±34.6	179.6±34.3	183.0±33.7	0.042
HDL cholesterol (mg/dL)	46.9±12.1	47.5±12.5	48.0±12.3	46.5±11.4	0.707
Total-to-HDL cholesterol ratio	4.0±1.1	4.0±1.1	4.0±1.2	4.1±1.1	0.108
Triglycerides (mg/dL)	124 (87–185)	122 (86–192)	133 (79–194)	135 (88–197)	0.060
Use of medication to treat hypertension, n (%)	216 (17.2)	142 (18.6)	47 (22.5)	100 (20.9)	0.036
Use of medication to treat dyslipidemia, n (%)	41 (3.3)	35 (4.6)	13 (6.2)	30 (6.3)	0.003
Alcohol consumption (drinks/day)	1.9±3.3	2.0±3.1	3.1±4.3	2.1±3.4	0.002
Current smoking, n (%)	431 (34.3)	231 (30.3)	65 (31.1)	135 (28.2)	0.013
Educational level, n (%)					0.079
Elementary school or lower	833 (66.3)	471 (61.8)	126 (60.3)	300 (62.6)	
Middle or high school	367 (29.2)	251 (33.0)	72 (34.4)	154 (32.2)	
College or higher	56 (4.5)	40 (5.2)	11 (5.3)	25 (5.2)	

BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment-insulin resistance; HDL, high-density lipoprotein.
Data are presented as means±standard deviations, or medians (with interquartile ranges) or numbers (with percentages). All participants were divided into non-snorers, occasional snorers (1–3 days/week), frequent snorers (4–6 days/week), and constant snorers (7 days/week).

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Table 2. Characteristics of the Female Study Population by Self-Reported Snoring Frequency (n=4080)

	Non-snorers (n=1966)	Occasional snorers (n=1188)	Frequent snorers (n=261)	Constant snorers (n=665)	*p* trend
Age (yr)	63.8±7.1	62.0±7.3	63.9±7.1	63.4±6.6	0.687
BMI (kg/m²)	23.7±3.0	24.7±3.0	25.1±3.0	25.7±3.3	<0.001
WC (cm)	84.3±8.6	86.5±8.4	87.9±8.2	89.1±9.1	<0.001
Systolic blood pressure (mm Hg)	123.7±18.9	124.8±18.5	125.6±18.2	126.2±18.2	0.003
Diastolic blood pressure (mm Hg)	79.0±10.3	79.7±10.2	79.6±10.2	80.4±10.3	0.005
HbA1c (%)	5.5±0.4	5.5±0.4	5.5±0.4	5.6±0.4	<0.001
FBG (mg/dL)	97.5±9.6	98.2±9.3	99.0±9.4	98.2±10.2	0.049
Insulin (μU/mL)	5.2±3.6	5.6±4.0	5.7±3.4	6.1±4.0	<0.001
HOMA-IR	1.3±0.9	1.4±1.0	1.4±0.9	1.5±1.1	<0.001
Total cholesterol (mg/dL)	191.9±35.8	194.0±36.4	195.6±36.0	194.8±36.7	0.066
HDL cholesterol (mg/dL)	48.1±11.3	48.5±11.1	49.2±12.2	47.8±11.6	0.904
Total-to-HDL cholesterol ratio	4.2±1.1	4.2±1.1	4.3±2.3	4.3±1.1	0.037
Triglycerides (mg/dL)	122 (86–177)	126 (86–179)	136 (98–188)	137 (96–193)	<0.001
Use of medication to treat hypertension, n (%)	374 (19.0)	275 (23.1)	86 (33.0)	205 (30.8)	<0.001
Use of medication to treat dyslipidemia, n (%)	93 (4.7)	73 (6.1)	17 (6.5)	44 (6.6)	0.156
Alcohol consumption (drinks/day)	0.1±0.5	0.1±0.5	0.2±0.8	0.1±0.5	0.015
Current smoking, n (%)	76 (3.9)	48 (4.0)	8 (3.1)	23 (3.5)	0.560
Educational level, n (%)					0.973
Elementary school or lower	1762 (89.6)	1003 (84.4)	238 (91.2)	596 (89.6)	
Middle or high school	192 (9.8)	169 (14.2)	22 (8.4)	66 (9.9)	
College or higher	12 (0.6)	16 (1.4)	1 (0.4)	3 (0.5)	

BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment-insulin resistance; HDL, high-density lipoprotein.
Data are presented as means±standard deviations, or medians (with interquartile ranges) or numbers (with percentages). All participants were divided into non-snorers, occasional snorers (1–3 days/week), frequent snorers (4–6 days/week), and constant snorers (7 days/week).

Table 3. Correlations between Snoring Frequency and Blood Glucose Control Indicators

	HbA1c (%)		FBG (mg/dL)		Insulin (μU/mL)		HOMA-IR	
	r	*p*	r	*p*	r	*p*	r	*p*
Males	0.007	0.731	0.054	0.005	0.072	<0.001	0.072	<0.001
Females	0.080	<0.001	0.034	0.031	0.093	<0.001	0.093	<0.001

HbA1c, hemoglobin A1c; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment-insulin resistance.

2. Fully adjusted HbA1c concentrations of constant snorers were significantly higher than those of non-snorers. In model 3, the fully adjusted mean (95% CI) HbA1c concentrations for non-snorers and occasional, frequent, and constant snorers were 5.53% (5.47–5.59%), 5.53% (5.47–5.59%), 5.57% (5.49–5.64%), and 5.57% (5.51–5.64%), respectively, reflecting a dose-response relationship (*p* trend=0.004). In both genders, a dose-response relationship between snoring frequency and HOMA-IR concentration was detected in models 1 and 2. However, after further adjustment for BMI and WC in model 3, the association between snoring and HOMA-IR was no longer significant in males (*p* trend=0.801) or females (*p* trend=0.630).

Association between snoring and elevated HbA1c and HOMA-IR levels

The relationships between snoring frequency and elevated HbA1c and HOMA-IR levels are shown in Table 5. After adjusting for age (model 1), the ORs for elevated HbA1c levels were not significantly higher or lower for occasional, frequent, or constant male snorers than for non-snorers. In males, no significant relationship between snoring frequency and an elevated HbA1c level was apparent in either model 2 or 3. In contrast, the ORs for an elevated HbA1c level were significantly higher for females who snored frequently (OR 1.54, 95% CI 1.11–2.15) or constantly (OR 1.65, 95% CI 1.31–2.07) than for non-snorers (model 1). After further adjustment, the ORs for elevated HbA1c levels in females who snored constantly remained significant (OR 1.45, 95% CI 1.22–1.95 in model 2; OR 1.30, 95% CI 1.02–1.66 in model 3). For females only, significant linear trends were evident in all of models 1, 2, and 3.

Although a dose-response relationship between snoring frequency and elevated HOMA-IR level was observed in males in model 1, the significant association disappeared after further adjustment in models 2 and 3. In females, a dose-response

Table 4. Gender-Specific HbA1c and HOMA-IR Levels by Snoring Frequency Derived Using a General Llinear Model

	Model 1*		Model 2†		Model 3‡	
	Mean (95% CI)	*p*	Mean (95% CI)	*p*	Mean (95% CI)	*p*
HbA1c						
Males						
Non-snorers	5.47 (5.44–5.49)		5.49 (5.44–5.53)		5.49 (5.44–5.53)	
Occasional snorers	5.47 (5.44–5.50)	0.899	5.49 (5.45–5.54)	0.775	5.49 (5.44–5.54)	0.943
Frequent snorers	5.44 (5.39–5.50)	0.436	5.47 (5.40–5.53)	0.433	5.46 (5.39–5.52)	0.330
Constant snorers	5.49 (5.45–5.53)	0.284	5.51 (5.46–5.56)	0.340	5.50 (5.45–5.55)	0.546
p for trend	0.544		0.648		0.904	
Females						
Non-snorers	5.46 (5.45–5.48)		5.52 (5.46–5.58)		5.53 (5.47–5.59)	
Occasional snorers	5.48 (5.46–5.50)	0.223	5.53 (5.47–5.60)	0.432	5.53 (5.47–5.59)	0.982
Frequent snorers	5.53 (5.49–5.58)	0.007	5.58 (5.50–5.65)	0.035	5.57 (5.49–5.64)	0.138
Constant snorers	5.55 (5.52–5.58)	<0.001	5.59 (5.53–5.66)	<0.001	5.57 (5.51–5.64)	0.011
p for trend	<0.001		<0.001		0.004	
HOMA-IR						
Males						
Non-snorers	1.10 (1.05–1.16)		1.35 (1.24–1.46)		1.32 (1.21–1.42)	
Occasional snorers	1.20 (1.13–1.27)	0.033	1.44 (1.32–1.56)	0.048	1.36 (1.24–1.47)	0.363
Frequent snorers	1.22 (1.09–1.36)	0.106	1.44 (1.28–1.60)	0.212	1.34 (1.18–1.49)	0.787
Constant snorers	1.27 (1.18–1.36)	0.003	1.46 (1.34–1.59)	0.030	1.34 (1.22–1.46)	0.679
p for trend	0.004		0.049		0.801	
Females						
Non-snorers	1.26 (1.22–1.31)		1.51 (1.36–1.66)		1.52 (1.38–1.66)	
Occasional snorers	1.38 (1.32–1.44)	0.002	1.58 (1.43–1.73)	0.036	1.52 (1.37–1.66)	0.870
Frequent snorers	1.42 (1.30–1.54)	0.017	1.59 (1.40–1.77)	0.215	1.48 (1.30–1.65)	0.471
Constant snorers	1.52 (1.45–1.60)	<0.001	1.68 (1.52–1.84)	<0.001	1.51 (1.36–1.67)	0.812
p for trend	<0.001		<0.001		0.630	

HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment-insulin resistance, CI, confidence interval; BMI, body mass index; WC, waist circumference.
Data are presented as mean (95% CI). All participants were divided into non-snorers, occasional snorers (1–3 days/week), frequent snorers (4–6 days/week), and constant snorers (7 days/week).
*Adjusted for age, †Adjusted for age, educational level, systolic blood pressure, total-to-high density lipoprotein cholesterol ratio, triglyceride level, current smoking, alcohol consumption, use of medication to treat hypertension, and use of medication to treat dyslipidemia, ‡Adjusted for the variables of model 2 plus BMI and WC.

relationship between snoring frequency and elevated HOMA-IR level was detected in models 1 and 2. However, after further adjustment for BMI and WC in model 3, no significant association between snoring and elevated HOMA-IR level was evident in females.

DISCUSSION

We explored gender-specific cross-sectional associations between self-reported snoring frequency with HbA1c and HOMA-IR levels in a healthy population, aged ≥50 years, without DM. We found that more frequent snoring was significantly associated with increased HbA1c levels among females without DM but not males; the association remained consistent after adjustment for covariates.

Earlier epidemiological studies examined the association between self-reported snoring and DM, although the results were inconsistent. A recent meta-analysis found a significant relationship between habitual snoring and DM; the association was strong in females but not in males.[15] Although the detailed mechanism of the association between snoring and DM remains poorly understood, biological causes have been suggested. Intermittent hypoxia and hypercapnia developing during snoring may stimulate sympathetic activity, induce oxidative stress, increase the levels of counter-regulatory hormones, and activate pro-inflammatory cytokines, contributing to the pathogenesis of DM by increasing insulin resistance.[17,18] In addition, the close relationships between snoring and both subclinical atherosclerosis and cardiovascular disease may trigger the development of DM.[7]

It was important to explore the association between snoring and HbA1c level in individuals without DM, as higher HbA1c levels are indicative of poor glycemic control, suggesting that DM may be developing.[19] However, although many studies have explored the association between snoring and DM, only a few

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Table 5. Gender-Specific Risk for Elevated HbA1c and HOMA-IR Levels by Snoring Frequency, Derived Using Logistic Regression

	Model 1*	Model 2†	Model 3‡
Elevated HbA1c (top quintile, ≥5.9%)			
Males			
Non-snorers	1.00	1.00	1.00
Occasional snorers	0.88 (0.68–1.14)	0.88 (0.68–1.15)	0.87 (0.67–1.13)
Frequent snorers	0.77 (0.49–1.19)	0.76 (0.48–1.18)	0.73 (0.47–1.15)
Constant snorers	1.12 (0.85–1.49)	1.11 (0.83–1.48)	1.07 (0.80–1.43)
p for trend	0.693	0.754	0.948
Females			
Non-snorers	1.00	1.00	1.00
Occasional snorers	1.17 (0.96–1.44)	1.15 (0.93–1.42)	1.07 (0.87–1.33)
Frequent snorers	1.54 (1.11–2.15)	1.42 (1.01–2.01)	1.31 (0.93–1.85)
Constant snorers	1.65 (1.31–2.07)	1.45 (1.22–1.95)	1.30 (1.02–1.66)
p for trend	<0.001	<0.001	0.019
Elevated HOMA-IR (top quintile, ≥1.74)			
Males			
Non-snorers	1.00	1.00	1.00
Occasional snorers	1.24 (0.97–1.58)	1.21 (0.94–1.56)	1.08 (0.83–1.41)
Frequent snorers	1.40 (0.96–2.04)	1.27 (0.85–1.89)	1.08 (0.71–1.65)
Constant snorers	1.38 (1.05–1.82)	1.21 (0.90–1.62)	0.93 (0.68–1.27)
p for trend	0.012	0.156	0.729
Females			
Non-snorers	1.00	1.00	1.00
Occasional snorers	1.24 (1.04–1.48)	1.14 (0.95–1.37)	0.95 (0.78–1.15)
Frequent snorers	1.40 (1.04–1.90)	1.19 (0.86–1.64)	0.89 (0.63–1.25)
Constant snorers	1.73 (1.41–2.12)	1.48 (1.19–1.82)	0.93 (0.74–1.17)
p for trend	<0.001	<0.001	0.449

HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment-insulin resistance; OR, odds ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference.
Data are presented as OR (95% CI). All participants were divided into non-snorers, occasional snorers (1–3 days/week), frequent snorers (4–6 days/week), and constant snorers (7 days/week).
*Adjusted for age, †Adjusted for age, educational level, systolic blood pressure, total-to-high density lipoprotein cholesterol ratio, triglyceride level, current smoking, alcohol consumption, use of medication to treat hypertension, and use of medication to treat dyslipidemia, ‡Adjusted for the variables of model 2 plus BMI and WC.

epidemiological works have examined the association between snoring and HbA1c levels in populations without DM. Again, the findings have been inconsistent.[20,21] The Korean Health and Genome Study on non-obese normoglycemic adults found that habitual snoring was significantly associated with elevated HbA1c levels (5.8%; the top quintile) in both males and premenopausal females, but not in postmenopausal females. However, the results were not adjusted in terms of FBG or insulin levels.[20] One large American study of adults without DM found that snoring frequency was positively associated with both insulin and HbA1c levels. However, gender-specific associations may not have been explored: all analyses were run on a population including both males and females.[21] The Korean Multi-Rural Communities Cohort Study found that more frequent snoring was significantly associated with elevated FBG levels (≥100 mg/dL). However, DM patients currently on medication were included and their elevated FBG levels would have affected the analyses.[2] In the present study, we excluded patients with DM; we explored the association between snoring and HbA1c levels in only adults without DM (thus those who were normal or had prediabetes).

In contrast to what was previously found,[20] we showed that habitual snoring was significantly associated with increased HbA1c levels in females but not males. Interestingly, this gender-specific association was similar to that found between snoring and DM in a prior meta-analysis; the association was significant in females but not males.[15] We found that, even in females without current DM, habitual snoring was associated with poor glycemic control, which may increase the risk of DM development and subsequent cardiovascular disease. It is not clear why the association between snoring and HbA1c level among adults without DM differs by gender, although hormones may play a role. Sleep-disordered breathing and diabetes are both affected by sex steroid hormones. In females, sleep-disordered breathing increases after menopause and can be alleviated by hormone replacement therapy.[22,23] Females with polycystic ovary syndrome often develop DM and suffer from sleep apnea.[24,25] The presence of polycystic ovary syndrome in premenopausal females may partially explain gender differences in the association between snoring and HbA1c.[26] Because males have a higher risk for cardiovascular disease than females, it is possible that males with severe snoring may have passed away at a younger age and been less likely to be included in the study. There is also the possibility of a gender bias in the classification of self-reported snoring frequency. Lastly, confounders not accounted for in this study may have influenced outcomes. Further studies are needed to explore whether snoring is significantly associated with HbA1c levels in either gender.

Obesity is associated with snoring and sleep apnea.[27,28] There are also strong associations of obesity with type 2 diabetes and impaired glucose tolerance.[29,30] In this study, we assessed the association between snoring and HbA1c level independent of obesity, which is a potent risk factor for hyperglycemia and increased HbA1c. After adjustment for BMI and WC in model 3, the OR for elevated HbA1c levels in females who snored constantly was slightly attenuated, but remained significant. Therefore, although obesity influences HbA1c levels, a significant association between snoring and HbA1c was identified independent of obesity. However, the significant dose-response relationship between snoring frequency and elevated HOMA-IR disappeared after further adjustment for obesity indices, such as BMI and WC, in females. The exact underlying mechanism is unknown; however, the following is a possible explanation. HOMA-IR is used to qualify insulin resistance, and obesity is a risk factor for insulin resistance,[31,32] implying a cause-and-effect relationship.[33,34] It is possible that obesity indices confound the association between snoring frequency and elevated HOMA-IR. In this study, controlling for the potential confounding effect of obesity may in fact reveal no association between snoring and elevated HOMA-IR in females.

Our study had certain limitations. First, the cross-sectional design renders it impossible to draw causal inferences between snoring and outcome variables. Nevertheless, several studies have addressed direct causal relationships. Snoring-induced hypoxia and hypercapnia can stimulate sympathetic activity and increase plasma catecholamine and cortisol levels, thereby impairing glucose homeostasis and causing insulin resistance.[35-37] In addition, the formation of reactive oxygen species with intermittent hypoxia increases the secretion of proinflammatory cytokines, which may mediate peripheral insulin resistance and induce diabetes.[17,38] Second, snoring data were obtained via a questionnaire; polysomnography would have been more objective. Finally, snorers who live or sleep alone are often unaware of their snoring status. This means that misclassification bias may have attenuated the association between snoring and HbA1c level. Despite these limitations, our work is valuable in that it increases our understanding of the gender-specific association between snoring status and HbA1c levels in large general populations.

In conclusion, we found that, in a healthy general population without DM, habitual self-reported snoring was positively associated with elevated HbA1c levels in females but not in males. This finding may influence the early management and treatment of sleep disorders, as individuals with prediabetes and increased HbA1c levels are more likely to develop DM. Further prospective studies are required to explore gender-specific differences in the association between snoring and HbA1c levels in large general populations.

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REFERENCES

1. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. Proc Am Thorac Soc 2008;5:207-17.
2. Shin MH, Kweon SS, Choi BY, Kim MK, Chun BY, Shin DH, et al. Self-reported snoring and metabolic syndrome: the Korean Multi-Rural Communities Cohort Study. Sleep Breath 2014;18:423-30.
3. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
4. 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.
5. Nagayoshi M, Tanigawa T, Yamagishi K, Sakurai S, Kitamura A, Kiyama M, et al. Self-reported snoring frequency and incidence of cardiovascular disease: the Circulatory Risk in Communities Study (CIRCS). J Epidemiol 2012;22:295-301.
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. Lee YH, Kweon SS, Choi BY, Kim MK, Chun BY, Shin DH, et al. Self-reported snoring and carotid atherosclerosis in middle-aged and older adults: the Korean Multi-Rural Communities Cohort Study. J Epidemiol 2014;24:281-6.
8. Lee SA, Amis TC, Byth K, Larcos G, Kairaitis K, Robinson TD, et al. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep 2008;31:1207-13.
9. Elley CR, Kenealy T, Robinson E, Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. Diabet Med 2008;25:1295-301.
10. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated hemoglobin in relationship to cardiovascular outcomes and death in patients with type 2 diabetes: a systematic review and meta-analysis. PLoS One 2012;7:e42551.
11. Lee YH, Shin MH, Choi JS, Rhee JA, Nam HS, Jeong SK, et al. HbA1c is significantly associated with arterial stiffness but not with carotid atherosclerosis in a community-based population without type 2 diabetes: The Dong-gu study. Atherosclerosis 2016;247:1-6.
12. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.
13. Garg N, Moorthy N, Kapoor A, Tewari S, Kumar S, Sinha A, et al. Hemoglobin A(1c) in nondiabetic patients: an independent predictor of coronary artery disease and its severity. Mayo Clin Proc 2014;89:908-16.

14. Pang KP, Terris DJ. Screening for obstructive sleep apnea: an evidence-based analysis. Am J Otolaryngol 2006;27:112-8.
15. Xiong X, Zhong A, Xu H, Wang C. Association between self-reported habitual snoring and diabetes mellitus: a systemic review and meta-analysis. J Diabetes Res 2016;2016:1958981.
16. Kweon SS, Shin MH, Jeong SK, Nam HS, Lee YH, Park KS, et al. Cohort profile: The Namwon Study and the Dong-gu Study. Int J Epidemiol 2014;43:558-67.
17. Alam I, Lewis K, Stephens JW, Baxter JN. Obesity, metabolic syndrome and sleep apnoea: all pro-inflammatory states. Obes Rev 2007;8:119-27.
18. Drager LF, Jun JC, Polotsky VY. Metabolic consequences of intermittent hypoxia: relevance to obstructive sleep apnea. Best Pract Res Clin Endocrinol Metab 2010;24:843-51.
19. Bennett CM, Guo M, Dharmage SC. HbA(1c) as a screening tool for detection of type 2 diabetes: a systematic review. Diabet Med 2007; 24:333-43.
20. Joo S, Lee S, Choi HA, Kim J, Kim E, Kimm K, et al. Habitual snoring is associated with elevated hemoglobin A1c levels in non-obese middle-aged adults. J Sleep Res 2006;15:437-44.
21. Ford ES, Wheaton AG, Chapman DP, Li C, Perry GS, Croft JB. Associations between self-reported sleep duration and sleeping disorder with concentrations of fasting and 2-h glucose, insulin, and glycosylated hemoglobin among adults without diagnosed diabetes. J Diabetes 2014;6:338-50.
22. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, et al. Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med 2003;167:1186-92.
23. 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.
24. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab 2001;86:517-20.
25. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2001;86:1175-80.
26. Valham F, Stegmayr B, Eriksson M, Hägg E, Lindberg E, Franklin KA. Snoring and witnessed sleep apnea is related to diabetes mellitus in women. Sleep Med 2009;10:112-7.
27. Xiao Q, Gu F, Caporaso N, Matthews CE. Relationship between sleep characteristics and measures of body size and composition in a nationally-representative sample. BMC Obes 2016;3:48.
28. Franklin KA, Sahlin C, Stenlund H, Lindberg E. Sleep apnoea is a common occurrence in females. Eur Respir J 2013;41:610-5.
29. Hayashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahn SE, et al. Visceral adiposity and the risk of impaired glucose tolerance: a prospective study among Japanese Americans. Diabetes Care 2003;26:650-5.
30. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L. Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. Diabetes Care 2000;23:465-71.
31. Lim SM, Choi DP, Rhee Y, Kim HC. Association between obesity indices and insulin resistance among healthy Korean adolescents: The JS High School Study. PLoS One 2015;10:e0125238.
32. Lee HJ, Shin G, Park SH, Cho HK. Insulin resistance and visceral fat obesity in hyperlipidemia. Korean Circulation J 1999;29:673-9.
33. Bak JF, Møller N, Schmitz O, Saaek A, Pedersen O. In vivo insulin action and muscle glycogen synthase activity in type 2 (non-insulin-dependent) diabetes mellitus: effects of diet treatment. Diabetologia 1992;35:777-84.
34. Freidenberg GR, Reichart D, Olefsky JM, Henry RR. Reversibility of defective adipocyte insulin receptor kinase activity in non-insulin-dependent diabetes mellitus. Effect of weight loss. J Clin Invest 1988;82:1398-406.
35. Iiyori N, Alonso LC, Li J, Sanders MH, Garcia-Ocana A, O'Doherty RM, et al. Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. Am J Respir Crit Care Med 2007;175:851-7.
36. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. Sleep 2003;26:15-9.
37. Marshall S, Garvey WT, Traxinger RR. New insights into the metabolic regulation of insulin action and insulin resistance: role of glucose and amino acids. FASEB J 1991;5:3031-6.
38. Sun L, Pan A, Yu Z, Li H, Shi A, Yu D, et al. Snoring, inflammatory markers, adipokines and metabolic syndrome in apparently healthy Chinese. PLoS One 2011;6:e27515.