## **Epidemiology**

# Snoring as an Independent Risk Factor for Hypertension in the Nonobese Population: The Korean Health and Genome Study

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**Background:** Although the close relationship between sleep-disordered breathing and hypertension has been strengthened by the accumulated evidence, the issues of controlling for coexisting factors and the lack of definite evidence in presenting a cause-effect relationship still remain. This study aimed to evaluate the independent association between habitual snoring and the 2-year incidence of hypertension in a nonobese population in Korea.

**Methods:** Subjects were drawn from the Korean Health and Genome Study, which is an ongoing population-based prospective study of Korean adults aged 40 to 69 years. The final sample comprised 2730 men and 2723 women without obesity and hypertension at the time of their initial examinations. All participants were reevaluated after an interval of 2 years. Hypertension was defined on the basis of blood pressure  $\geq$ 140/90 mm Hg or the use of antihypertensive medications. Habitual snorers were defined as those who snored  $\geq$ 4 days per week.

fter the earliest epidemiological data revealed a correlation between snoring and circulatory or cardiac disturbances about 3 decades ago,<sup>1,2</sup> there has been growing interest in the adverse effects of sleep-disordered breathing (SDB), which includes habitual snoring and sleep apnea syndromes, on cardiovascular morbidities. Hypertension and its deleterious consequences are well-known major risk factors for cardiovascular morbidity and mortality,<sup>3,4</sup> and so many researchers over the past few decades have investigated whether various types of SDB increase the risk for hypertension.<sup>5,6</sup> Although the close relationship between SDB and hypertension has been strengthened by the accumulated evi-

hypertension in every stratum of confounding factors, including age, sex, smoking, and level of blood pressure and body mass index at baseline, except for age ≥60 years. After adjustments of other covariates, habitual snoring was independently associated with a 1.49-fold and 1.56-fold excess for odds ratios of the 2-year incidence of hypertension in men and women, respectively.
 Conclusions: Although further evidence is needed, our results support the contention that habitual snoring is an important predisposing factor in future hypertension,

**Results:** Habitual snoring was significantly associ-

ated with increased odds ratios of the incidence rate of

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dence,<sup>7,8</sup> there is still no consensus about several issues.<sup>6,9,10</sup> The confounding effect of strong coexisting factors, such as obesity and smoking, has often been debated in discussions on the independent association between SDB and hypertension. In addition, there is still a lack of definite evidence supporting the cause-effect relationship and SDB, and especially habitual snoring, on hypertension.

International health research is focusing on subclinical conditions that precede serious diseases.<sup>11</sup> Habitual snoring, which repeatedly partially obstructs the upper airway during sleep, is regarded as a preclinical condition for sleep apnea syndrome, which may cause future cardiovas-

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cular morbidity,<sup>7,12</sup> and habitual snoring is quite prevalent in the general adult population around the world.<sup>13,14</sup> Furthermore, recent papers suggest that habitual snoring, irrespective of obstructive sleep apnea (OSA), may have an impact on developing cardiovascular disease because of the repeated local inflammation caused by snoring-induced vibrations.<sup>15,16</sup> Nevertheless, only a few prospective studies on the relationship between habitual snoring and the risk of developing hypertension have been performed.<sup>17,18</sup> The present study was prospectively performed to evaluate the independent association between habitual snoring and the 2-year incidence of hypertension in a nonobese sample of a population-based Korean cohort study.

## Methods Study Population

Subjects of the present study are participants in the Korean Health and Genome Study (KHGS), which is an ongoing, population-based, prospective study of Korean adults (age range, 40 to 69 years) that began in 2001. Physical examinations and assessments by questionnaires have been conducted for participants at an interval of every 2 years. The purpose of the KHGS is to investigate the frequency and incidence of chronic diseases and their relationships with potential risk factors or lifestyles. Previous cross-sectional investigations of data from the KHGS have been published.<sup>19,20</sup>

Baseline examinations of the KHGS were performed from 2001 to 2002 on 10,038 randomly selected participants. These participants consisted of 4763 men and 5275 women. Information on their general characteristics, lifestyle, sleep-related factors, health status, and current medications was assessed by trained interviewers. An initial round of physical examinations, which included blood pressure (BP), anthropometric measurements, and blood sampling, was conducted. Written consent was obtained from all participants at their first visit. Thereafter, all participants were contacted every year via telephone by the interviewer in charge, and they were encouraged to undergo reexamination every 2 years. After excluding those subjects who died during the follow-up period (n =68) and those who refused to participate or who could not be contacted (n = 1367), 8603 subjects were included in the 2-year follow-up study from 2003 to 2004. The overall follow-up rate was 86.2%. The mean duration of the follow-up period was  $1.8 \pm 0.2$  (SD) years.

For this study, we excluded those individuals who were classified as hypertensive (ie, those with BP  $\geq$ 140/90 mm Hg or who were taking an antihypertensive medication) or who provided incomplete information on their hypertension and snoring. To eliminate the likelihood of any confounding effect of obesity on the relationship between habitual snoring and hypertension, we excluded those individuals with a high body mass index (BMI) at the level of 27.5 kg/m<sup>2</sup> or over. The cutoff point of high BMI was

determined on the basis of recent WHO recommendations for Asian populations.<sup>21</sup> Finally, 2730 men and 2723 women without obesity and hypertension at the time of their initial examinations were included in this study.

#### Measurement of BP

Measurements of BP were performed using mercury sphygmomanometers (Baumanometer; W.A. Baum, Copiague, NY) at both examinations by trained technicians, according to a standardized protocol.<sup>22</sup> All measurements were taken after at least a 5-min rest period, and the phase V Korotkoff sounds were used as a diastolic point. The BP measurements of participants were repeated twice after a 30-sec interval, and these were recorded to the nearest 2 mm Hg. The average value of the readings was used as a measure of systolic and diastolic BP. Hypertension was defined either when the systolic and diastolic BPs were  $\geq$ 140 and  $\geq$ 90 mm Hg, respectively, or when a study participant was being treated with antihypertensive medications. At the 2-year follow-up evaluation, the medical histories of the previous 2 years were collected, and the BPs of participants were evaluated by the same observers. Finally, hypertension was determined in the same manner as during baseline examinations.

#### **Habitual Snoring**

As part of the interview, participants were asked, "Have you ever heard that you snored?" Subjects could answer on a 5-point scale: "never," "occasionally," "sometimes (1 to 3 times a week)," "often (4 to 6 times a week)," and "every night." Habitual snoring was defined as the answers "often" or "every night." To determine the test-retest reliability of the questionnaire, 200 participants were retested 4 weeks after the first test; the kappa value for the question on snoring was 0.73. Furthermore, to estimate the association between habitual snoring and OSA, 457 participants in the KHGS were invited to undergo an overnight sleep study using a computerized polysomnography system (Alice 4; Respironics, Atlanta, GA).<sup>23</sup> As a result, 55% of habitual snorers (HSs) had OSA with an apneahypopnea index (AHI)  $\geq$ 5.

#### Other Measurements

Subjects were asked about their demographic, medical, and behavioral characteristics by trained interviewers. The information that was recorded included age, sex, the status of subjects' cigarette smoking and alcohol intake, and regular exercise ( $\geq 2$  times/week and  $\geq 30$ min at a time). The changing rate of body weight at the 2-year follow-up study, as compared with the baseline examination, was divided into four categories based on quartiles: (1)  $\geq 2.0\%$ , (2) 0.0% to 2.0%, (3) -2.0% to 0.0%, and (4) <2.0%. To obtain lipid levels, blood was drawn from a vein after a 10-h fast. Triglycerides, total cholesterol, and HDL cholesterol were measured with an ADVIA 1650 system (Bayer, Tarrytown, NY). Hypertriglyceridemia was defined by the criteria of the Adult Treatment Panel III, ie, a triglyceride level  $\geq 150 \text{ mg/dL.}^{24}$ 

#### **Statistical Methods**

The sex-specific baseline characteristics of the study sample were expressed as mean and standard deviations (median and interquartile ranges) or as frequency and percentages. Characteristics at the baseline examination that differed between subjects with and without habitual snoring were compared by *t*-test, Mann-Whitney *U* test, and  $\chi^2$  test. Paired *t*-tests were performed to compare the variation in BP from baseline to the 2-year follow-up examination. The crude odds ratios of the 2-year incidence of hypertension were estimated in each subgroup of confounding factors. The age-, BMI-, and other risk factor-adjusted odds ratios were also estimated by multivariate logistic regression analyses. The reported *P* values were based on two-sided levels of significance. Statistical analyses were performed with SAS Enterprise Guide 3.0 software (SAS Institute, Cary, NC).

### Results

Table 1 compares the general characteristics of HSs and non-HSs for men and women, respectively. Among the subjects of the present study, 14.4% of the men and 9.0% of the women snored  $\geq$ 4 days a week. Even though obese subjects who had a higher BMI ( $\geq$ 27.5 kg/m<sup>2</sup>) were excluded from this study, the baseline BMI of HSs was slightly higher than that of non-HSs for both men and women. According to the measurements of BP and lipids, the non-HS subjects had a tendency to be healthier than the HSs. Any factors related to lifestyle were not significantly different between HSs and non-HSs.

To illustrate the change in BP over the 2 years, the systolic and diastolic BPs of male HSs and female HSs



**FIG. 1.** Level of the blood pressures of habitual snorers (HSs) and non-HSs at baseline and at 2-year follow-up examinations.

and non-HSs are depicted in Fig. 1. Among men, the changes in diastolic BP during the 2-year follow-up were greater for HSs than for non-HSs, although the differences were not statistically significant (P = .0583). This trend was not observed among the women.

**Table 1.** Comparisons of general characteristics at baseline examination between habitual snorers

 and nonsnorers\*

	Men		Women	
<b>Baseline characteristics</b>	HS	Non-HS	HS	Non-HS
Number of subjects	393	2337	244	2479
Age (y)	$51.2 \pm 8.1$	$51.5 \pm 8.9$	$54.8 \pm 8.5$	$50.6 \pm 8.78$
Body mass index (kg/m <sup>2</sup> )	$24.1 \pm 2.2$	$23.3 \pm 2.4$ §	$24.3 \pm 2.0$	$23.5 \pm 2.3$ §
Rate of changes in body weight over		-		-
2 years (%)	$-0.38 \pm 5.45$	0.27 ± 4.65‡	0.27 ± 4.24	$0.29 \pm 5.16$
Systolic BP (mm Hg)	$112 \pm 12$	$112 \pm 12$	$113 \pm 13$	$109 \pm 138$
Diastolic BP (mm Hg)	74 ± 9	73 ± 9†	72 ± 8	70 ± 98
Total cholesterol (mg/dL)	$197.3 \pm 34.9$	195.2 ± 35.7	$200.1 \pm 34.7$	$194.1 \pm 34.7 \pm$
HDL cholesterol (mg/dL)	$45.0 \pm 11.0$	$47.0 \pm 15.0 \ddagger$	$48.0 \pm 15.0$	$51.0 \pm 15.0 \pm$
Triglycerides (mg/dL)	$130.0 \pm 101.0$	126.0 ± 91.0	$118.5 \pm 71.0$	$102.0 \pm 72.0$ §
Alcohol consumption (%)	71.4	70.6	26.0	27.6
Smoking cigarettes (%)	52.4	50.8	3.3	3.5
Regular exercise (%)¶	27.7	24.3	23.4	25.5

BP = blood pressure; HSs = habitual snorers; non-HSs = nonsnorers.

\* Values are mean  $\pm$  standard deviation; † Significantly different from HS (P < .05); ‡ Significantly different from HS (P < .01); § Significantly different from HS (P < .001); || Median  $\pm$  interquartile range; ¶ Defined as subjects exercising  $\geq 2$  days per week for  $\geq 30$  min.

		Odds ratios (95% confidence intervals)	
Factors	Subgroups	Non-HS	HS
Age groups	40–49 years	Reference	2.77 (1.85-4.14)
5 5 1	50–59	Reference	1.70 (1.15–2.51)
	60–69	Reference	1.02 (0.66–1.56)
Sex	Men	Reference	1.49 (1.10–2.03)
	Women	Reference	2.25 (1.58–3.19)
Baseline BP	<120/80 mm Hg	Reference	1.39 (1.02–1.89)
	120/80-139/89	Reference	2.15 (1.46–3.18)
Baseline BMI	<23.0 kg/m <sup>2</sup>	Reference	1.64 (1.02–2.64)
	23.0–24.9	Reference	1.98 (1.32–2.98)
	25.0-27.4	Reference	1.51 (1.06–2.15)
Smoking	Smoker	Reference	1.64 (1.09–2.47)
5	Nonsmoker	Reference	1.82 (1.37–2.42)

Table 2.	Odds ratios of the incidence	e rate of hypertension in	each subgroup of	f confounding factors

BP = blood pressure; BMI = body mass index.

Table 2 lists the odds ratios of the incidence rate of hypertension in the subgroups of major confounding factors, including age, sex, level of BP and BMI at baseline, and smoking. Habitual snoring was significantly associated with increased odds ratios for the incidence rate of hypertension in every stratum of confounding factors, except for age  $\geq 60$  years.

In addition to age and BMI, other characteristics such as drinking, smoking, exercise, triglycerides, and the chang-

ing rate of body weight over the 2 years were introduced into a multivariate logistic regression model (Table 3). As a result, habitual snoring was independently associated with a 1.49fold and 1.56-fold increase of the odds ratios for the 2-year incidence of hypertension in men and women, respectively. An increase of  $\geq 2.0\%$  of body weight during the 2 years was also shown to be an independent risk factor for developing hypertension. Hypertriglyceridemia affected the 2-year incidence of hypertension for women only.

		Odds ratios (95% confidence intervals)		
Variables	Comparison groups	Adjusted for age and BMI	Adjusted for age, BMI, and other characteristics*	
Men				
Habitual snoring	Yes No	1.41 (1.02–1.93) Reference	1.49 (1.08–2.05) Reference	
Changing rate of body weight				
over 2 years†	$\geq 2.0\%$ 0.0-1.9% 7-2.0-0.0% $\leq 2.0\%$	1.56 (1.13–2.15) 1.17 (0.83–1.67) 0.88 (0.60–1.29) Reference	1.60 (1.12–2.16) 1.16 (0.82–1.65) 0.88 (0.60–1.29) Reference	
Triglycerides	≥150 mg/dL <150	1.23 (0.95–1.59) Reference	1.24 (0.96–1.61) Reference	
Women				
Habitual snoring	Yes No	1.55 (1.07–2.24) Reference	1.56 (1.07–2.27) Reference	
Changing rate of body weight				
over 2 years	≥2.0% 0.0–1.9% -2.0–0.0%	1.61 (1.15–2.26) 1.18 (0.81–1.71) 1.10 (0.73–1.65)	1.57 (1.12–2.22) 1.07 (0.73–1.57) 1.07 (0.71–1.62)	
Triglycerides	≤2.0% ≥150 mg/dL	Reference 1.60 (1.22–2.11)	Reference 1.55 (1.17–2.05)	
<i></i>	<150	Reference	Reference	

Tabla 2 Estimated odds ratios for 2-year incidence of hypertension

BMI = body mass index.

\* Alcohol consumption, smoking, exercise, and other variables; † Divided into quartiles.

## Discussion

The present study found that habitual snoring was an independent predisposing factor for developing hypertension after 2 years, even for nonobese men and women. The higher risk of habitual snoring in the 2-year incidence of hypertension was observed to be significant across every stratum of the covariates, except for subjects aged  $\geq 60$  years, and this was also independent of the known risk factors. These results were compatible with our earlier cross-sectional finding, which represented an independent association between habitual snoring and hypertension.<sup>20</sup>

Despite numerous studies that tried to examine any independent associations between SDB and hypertension,<sup>5,6,9,10</sup> a recent report stated that several questions remain regarding these relationships.<sup>25</sup> The first question is whether patients with SDB have an increased risk for the incidence of hypertension. To date, there is a scarcity of population-based evidence on this issue.9,10,13 Although a few studies prospectively followed the effect of SDB on developing hypertension, these studies had such limitations as small sample size, selection bias, uncontrolled covariates, or subjective definitions of hypertension.<sup>5,12</sup> Therefore, to identify the effect of habitual snoring on the 2-year incidence of hypertension, randomly selected KHGS participants without hypertension were enrolled in the present study and observed prospectively. Their BP was measured according to a standardized protocol at both baseline and 2-year follow-up examinations. The next question is whether obesity contributes to the relationship between SDB and hypertension. Because obesity is well known as a major coexisting factor for both hypertension and SDB, the issue of precisely adjusting or controlling for obesity has frequently been referred to and debated. Until recently, the failure to control for confounding factors was pointed out as a study limitation in many clinical and epidemiological studies.<sup>25</sup> In our current study, to eliminate the confounding effect of obesity, subjects with a high BMI (>27.5 kg/m<sup>2</sup>) at baseline examination were excluded, and BMI was adjusted as a continuous variable in the multivariate regression analysis model.

The predisposing effect of habitual snoring on the incidence rate of hypertension is supported by previous studies.<sup>10,17,18</sup> Lindberg et al performed the first prospective study on a causal relationship between snoring and hypertension.<sup>17</sup> In their study, the subjects with habitual snoring developed hypertension more frequently than did non-HS subjects. A significantly higher incidence of hypertension in HS subjects was also found, even when subjects were divided into subgroups according to BMI, smoking, alcohol dependence, and physical activity (but not age); this was consistent with our present results. Another 8-year prospective study on the association between snoring and the risk for hypertension was based on the data of the Nurses Health Study in the United States.<sup>18</sup> Those authors also found that habitual snoring was independently associated with a 1.55-fold increased odds ratio for hypertension in women. This is comparable with our current results, ie, a 1.49-fold increased odds ratio for men and a 1.56-fold increased odds ratio for women. Although those two representative prospective studies reported a positive association between habitual snoring and future hypertension, in a cross-sectional analysis of the Sleep Heart Health Study that included a large-scale multicenter sample, an independent association with hypertension was not observed for subjects who only snored.<sup>6</sup> Thus, although the present study was supportive of the hypothesis that habitual snoring could result in hypertension, further evaluations are warranted as to whether there is a definite causal relationship between habitual snoring and the later development of hypertension.

Currently, the putative mechanisms of snoring-induced hypertension or other cardiovascular morbidities are mainly explained by sympathetic activation and oxidative stress, which is caused by apneic episodes, since habitual snoring is thought to be closely related to sleep apnea.<sup>12,18,25</sup> It is widely held that activated hemodynamic responses to repeated apneic episodes elevate sympathetic activity and pulmonary artery pressure, and this may directly cause hypertension. In addition, other studies indicated that apnea-related hypoxia causes oxidative stress, and this may accelerate atherosclerosis in the coronary and intracranial arteries by increasing both superoxide production and the levels of circulating adhesion molecules and by decreasing fibrinolytic activity.<sup>26,27</sup> Moreover, regardless of the presence of OSA, the local inflammatory effect of snoring-induced vibrations on the pathogenesis of cardiovascular morbidities was suggested.<sup>15,16</sup> Puig et al provided evidence from their recent experimental study that high-frequency vibrations enhanced the release of interleukin-8, which is a proinflammatory cytokine that plays a significant role in systemic inflammation.<sup>16</sup> However, the underlying mechanisms have not been fully investigated, and further evaluation of the pathogenesis of snoringinduced hypertension is definitely needed.

As previously established, weight gain and being overweight comprise a major risk factor for the incidence of hypertension and other cardiovascular morbidities.<sup>28</sup> In the present study, an increase in body weight >2.0%during the preceding 2 years was independently associated with an increased risk for developing hypertension, compared with subjects with a decrease in body weight of >2.0%. In the present study, a higher level of triglycerides, which is known to be a cardiovascular risk factor,<sup>29</sup> was associated with a 1.55-fold excess of the odds ratio for hypertension in women only.

Regarding the measurement of habitual snoring, the weak point of the present study was that we used selfreported data on the existence and frequency of snoring. This subjective measurement may have resulted in some misclassifications, which could have affected the significance or magnitude of the effect of snoring on hypertension. However, in spite of the suggestion by the authors of one study on self-reported snoring that snoring is an indicator of SDB,<sup>30</sup> snoring is still regarded as a major symptom of OSA syndrome, and it has been employed as a useful measurement of SDB in many epidemiological studies.<sup>12,17,18</sup> In this study, we examined the test-retest reliability of the snoring variable, and we previously evaluated the prevalence of OSA by performing polysomnography for a subsample of KHGS participants.<sup>23</sup> In addition, the present results were derived from a 2-year follow-up study of the representative cohort study in Korea. Although it may be difficult to conclude that a causal relationship exists between habitual snoring and hypertension based on a short-term follow-up study, the participants in the present study and in the KHGS will be continually examined for further evaluation.

In conclusion, this study was a population-based, prospective study that examined the relationship between habitual snoring and the development of future hypertension. The major finding of this study was an increased risk for developing hypertension in both nonobese men and women who habitually snored, compared with non-HS subjects. Although further evidence is needed, the results of this study suggest that habitual snoring could be considered an important predisposing factor in hypertension.

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