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Increased risk for new-onset hypertension in midlife male snorers: The 14-year follow-up study

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Abstract

While the association between sleep-related breathing disorders such as snoring and hypertension has been well established, it still remains unclear whether the association differs by age and gender. Therefore, in this 14-year follow-up study, we examined the independent association between self-reported snoring and the incidence of hypertension by gender and age groups in a large cohort of Korean adults. A total of 4,954 adults, aged 40–69 years, free of hypertension at baseline were enrolled. Participants were divided into three groups based on a self-reported snoring frequency: never; occasional (snoring <4 nights per week); and habitual snorer (snoring ≥4 nights). At baseline and biennial follow-up visits, blood pressure was measured by trained examiners. Incident hypertension was defined as the first occurrence at any follow-up examination where the participants had blood pressure ≥140/90 mmHg or were being treated with antihypertensive medication. After adjusting for known cardiovascular risk factors, only in men aged ≤45 years was habitual snoring significantly associated with a 1.5 times higher risk for incident hypertension than never snoring. In this age group, habitual snoring was significantly associated with increased risk for the development of hypertension, regardless of the presence of excessive daytime sleepiness. In women, snoring was not significantly associated with hypertension incidence in any age group. The present study suggests that young male snorers may be at high risk for the future development of hypertension, which has important clinical implications for early detection and treatment of snoring to reduce the burden of cardiovascular disease.

KEYWORDS
cohort study, habitual snoring, hypertension, incidence, sleep-disordered breathing

1 | INTRODUCTION

Snoring is a common condition that occurs due to vibration of the soft tissues in the nasopharynx and oropharynx during sleep, affecting approximately one in two middle-aged and older adults (Counter & Wilson, 2004; Young et al., 1993). Snoring is also a major symptom for obstructive sleep apnea (OSA), characterized by cyclic partial or complete obstruction of the upper airway during sleep with consequent hypoxia and arousals that may result in future cardiovascular and metabolic alterations (Pack & Gislason, 2009; Young, Peppard, & Gottlieb, 2002).

In past decades, epidemiological studies have demonstrated a significant association between hypertension and sleep-disordered breathing (SDB), including snoring and OSA, independent of other cardiovascular risk factors (Kim et al., 2007; Marin et al., 2012; Thomas et al., 2006). Earlier prospective studies (Hu et al., 1999; Lindberg et al., 1998) showed that self-reported snorers were more likely to have short-term and long-term incident hypertension, compared with non-snorers. However, two representative sleep cohorts in the USA reported conflicting results on the long-term impact of OSA on the incidence of new-onset hypertension (O'Connor et al., 2009; Peppard, Young, Palta, & Skatrud, 2000). Further prospective studies are necessary to confirm causal associations between SDB and hypertension.

In addition, questions persist as to whether the association differs by age and sex. Gender differences in prevalence and severity of SDB have been reported consistently in many studies (Mohsenin, 2001; Quintana-Gallego et al., 2004; Resta et al., 2005). Snoring and OSA more frequently appear in men than women across different age groups (Lin, Davidson, & Ancoli-Israel, 2008; Quintana-Gallego et al., 2004; Young et al., 1993), and women tend to have milder OSA than men (Gabbay & Lavie, 2012; Resta et al., 2005). Although mechanisms underlying the gender differences have not been studied extensively, anatomical differences in the upper airway between genders, such as larger tongue and longer oropharynx in men than women, and hormonal effects on body composition and ventilation may contribute to gender differences in severity of SDB and physiological consequences (Hou, Jia, & Liu, 2010; Schwertz & Penckofer, 2001). In a study of 1,113 patients with OSA in China (Yu et al., 2014), a distinct association emerged between hypertension and OSA in that the prevalence of hypertension gradually increased with OSA severity in men, but no association emerged in women. However, earlier Western epidemiological studies reported that snoring increases risk for hypertension and other cardiovascular diseases in women (Dunai et al., 2008; Hu et al., 1999; Leineweber, Kecklund, Janszky, Akerstedt, & Orth-Gomer, 2004; Sands et al., 2013). Further prospective studies are needed to compare cardiovascular consequences of snoring and OSA between men and women, and possible ethnic differences.

Moreover, the link between SDB and hypertension is less clear in older adults than middle-aged populations. The Sleep Heart Health study suggested an age-dependent association between OSA and hypertension (Haas et al., 2005). The authors found that OSA was significantly associated with a higher risk of hypertension in middle-aged adults aged 40–59 years, but not in older adults (≥60 years). This result was consistent with our previous study in a Korean population (Kim et al., 2007), examining the association between self-reported snoring and the 2-year incidence of hypertension in middle-aged and older adults. The increased risk for hypertension disappeared in older adults aged 60 years or older. Whether SDB resulted in different cardiovascular consequences between age groups needs additional investigation.

Therefore, in this study, we examined the independent association between habitual snoring (snoring ≥4 nights per week) and the 14-year incidence of hypertension in a cohort of Korean middle-aged and older adults, free of high blood pressure (BP) at baseline. The purpose of this study was to investigate whether the association between habitual snoring and incidence of hypertension differs by age and gender in a Korean population.

2 | METHODS

2.1 | Study sample

This study was conducted in a random sample of 10,030 Korean men and women, aged 40–69 years old, who participated in the Korean Genome and Epidemiology Study (KoGES). The KoGES is an ongoing community-based cohort study to identify genetic, environmental and behavioural risk factors for the prevalence and incidence of chronic diseases in Korea that began in 2001–2002. Participants were randomly selected from a rural (ANSUNG) and an industrial city (ANSAN) of South Korea, and underwent comprehensive physical examinations and surveys of risk factors at baseline. Follow-up examinations have been performed in the same participants biennially for 14 years. All participants provided informed consent following institutional guidelines. This study was based upon the information and approval from Institutional Review Board of Korea University Ansan Hospital and Ajou University School of Medicine.

For this study, we excluded 3,070 participants who had been diagnosed with hypertension, defined as high BP (BP ≥ 140/90 mm Hg) or the use of antihypertensive medication, at baseline examination. One-hundred and fifty-one participants were excluded due to the incomplete data on BP and medication. One-hundred and eight participants were deceased during the 14 years of follow-up, and 1,747 participants have not participated in the follow-up study. Therefore, the final sample consisted of 2,338 men and 2,616 women.

2.2 | Hypertension

At baseline and biennial follow-up visits, BP was measured by trained examiners using an appropriately sized cuff and a mercury sphygmomanometer. The first and the fifth phases of Korotkoff sounds were used for systolic and diastolic BP, respectively. BP measurements were made after a rest period of at least 5 min in the sitting position, and repeated twice with a 30-s recovery period. The

values were recorded to the nearest 2 mmHg, and the average value of the two readings was used for analysis. The use of antihypertensive medication was assessed by an interviewer-administered questionnaire at baseline and follow-up visits. Incident hypertension was defined as the first occurrences at any follow-up examination where the participants had BP ≥ 140/90 mmHg or were being treated with antihypertensive medication.

2.3 | Snoring

The frequency of snoring was assessed by an interviewer-administered questionnaire on a scale of 0–4: "0 = never", "1 = occasionally", "2 = snoring 1~3 nights a week", "3 = snoring 4~6 nights a week", and "4 = almost every night". Participants were divided into three different groups: never snorer, occasional snorer, and habitual snorer. Habitual snorer was defined as those who reported that they snore at least 4 nights a week; occasional snorer was defined as those snoring less than 4 nights a week. The test–retest reliability of the question on snoring frequency was examined in a subset of total participants (n = 200) at an interval of 2 weeks. Agreement between the two occasions was substantial with a Kappa statistic value of 0.73. Among the sample, 83% replied with the same answer on both occasions.

2.4 | Covariates

Study participants were asked about age, sex, smoking status (current, former, or never smoker), alcohol consumption (current, former, or never drinker), regular exercise (yes or no), family history of hypertension (yes or no), presence of diabetes, and presence or past history of cardiovascular diseases (i.e. myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and cerebral vascular disease), and current medications. The family history questionnaire evaluated the presence of hypertension in parents, grandparents and siblings. We assessed daytime sleepiness with the Epworth Sleepiness Scale (ESS; Johns, 1991). Excessive daytime sleepiness (EDS) was indicated with a total score greater than 10. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Venous blood was drawn in the morning after an 8 hr fasting period to assay levels of lipids and glucose. Lipid profiles were measured enzymatically by the Advia 1650 system (Bayer, Leverkusen, Germany) at the certified commercial laboratory (Seoul Clinical Laboratories, Seoul, Korea).

2.5 | Statistical analysis

We presented data as mean and standard deviation for continuous variables, and frequencies and percentages for categorical variables. Significant differences in means among three groups with different snoring frequency were evaluated using the analysis of variance for quantitative variables and chi-square test for categorical variables. In addition, we used univariate and multivariate Cox proportional hazard models to estimate the Cox proportional hazard ratio (HR), and 95% confidence interval (CI) of occasional and habitual snoring for the incidence of hypertension. The Kaplan–Meier survival analysis was performed to compare survival distributions during 14 years among the three groups with different snoring frequencies. Kaplan–Meier curves were generated according to the snoring status, with days from baseline examination as the timescale and incident hypertension as the outcome. Furthermore, to examine whether the survival curves differ by the presence of EDS, we divided each group into two subgroups: those with and without EDS. The log rank test was used to compare the curves. Covariates for the multivariate models included age, BMI, sex, drinking and smoking habits, regular exercise, family history of hypertension, presence of diabetes, triglyceride, high-density lipoprotein (HDL) cholesterol and cardiovascular diseases. Statistical analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). p-values less than 0.05 were considered statistically significant.

3 | RESULTS

Table 1 shows baseline characteristics among three groups with different frequencies of snoring (never, occasional, and habitual snorer) in total participants and by gender. Frequency of snoring increased with age in women; however, the mean age of snorers was significantly lower than never snorers in men. In both genders, snorers were associated with a worse cardiovascular risk profile, such as higher BP, BMI and lipids, compared with never snorers. Family history of hypertension was significantly higher in snorers than in never snorers.

Table 2 shows the results of the Cox-proportion hazard models. The HRs for hypertension incidence were calculated separately by stratifying the age into four groups: (a) 40–45 years old; (b) 46–55 years old; (c) 56–65 years old; and (d) 66 years old or older, in total participants and by gender. Comparing among three groups, the significantly increased risks for hypertension in all snorers and in younger habitual snorers aged ≤45 years disappeared after adjusting for age, sex, BMI, family history of hypertension, smoking, exercise, drinking alcohol, triglyceride, HDL and diabetes. In women, no significant associations between snoring and hypertension incidence emerged after adjusting for the covariates. Only in men aged 40–45 years did the habitual snorers show significantly higher HRs (crude HR = 1.90, 95% CI: 1.41–2.55, $p < 0.0001$) for incident hypertension than the never snorers group. After adjusting for all the covariates, HR of habitual snorers was still 1.5-fold higher than the control group for incidence of hypertension.

Figure 1 shows the HR of habitual snorers for the 14-year incidence of hypertension, estimated at each year of age, by gender. Habitual snoring showed significant ($p < 0.05$) HRs for hypertension incidence only in men aged 45 years or younger, not in women. Figure 2 illustrates Kaplan–Meier survival curves for male study participants aged 40–45 years. To examine whether survival curves differed by severity of snoring, determined by the existence of EDS, we compared survival curves among never, occasional and habitual snorers with and without EDS. As shown, regardless of the presence

TABLE 1 Comparison of baseline characteristics among three groups with different frequency of snoring

Variables	Total	Never snorers	Occasional snorers	Habitual snorers	*p*-value
Total	*N* = 4,954	*N* = 2,109	*N* = 2,186	*N* = 659	
Age (years)	50.8 ± 8.5[a]	50.7 ± 8.7	50.3 ± 8.2	52.3 ± 8.3	<0.0001
Sex					
Female	2,616 (52.8%)[b]	1,245 (59.0%)	1,097 (50.2%)	274 (41.6%)	<0.0001
Regular exercise					
Yes	1,286 (26.0%)	499 (23.7%)	614 (28.1%)	173 (26.3%)	
Smoking					
Non-smoker	2,968 (59.9%)	1,365 (64.7%)	1,273 (58.2%)	330 (50.1%)	<0.0001
Past-smoker	745 (15.0%)	277 (13.1%)	345 (15.8%)	123 (18.7%)	
Occasional smokers	149 (3.0%)	60 (2.8%)	64 (2.9%)	25 (3.8%)	
Habitual smokers	1,092 (22.0%)	407 (19.3%)	504 (23.1%)	181 (27.5%)	
Drinking					
Non-drinker	2,293 (46.3%)	1,078 (51.1%)	949 (43.4%)	266 (40.4%)	<0.0001
Past-drinker	301 (6.1%)	130 (6.2%)	133 (6.1%)	38 (5.8%)	
Current drinker	2,360 (47.6%)	901 (42.7%)	1,104 (50.5%)	355 (53.9%)	
HTN family history					
Yes	863 (17.4%)	326 (15.5%)	412 (18.8%)	125 (19.0%)	0.0073
EDS					
ESS > 10	702 (14.2%)	250 (11.9%)	318 (14.5%)	134 (20.3%)	<0.0001
DM					
Yes	437 (8.8%)	154 (7.3%)	199 (9.1%)	84 (12.7%)	<0.0001
CVD					
Yes	92 (1.9%)	35 (1.7%)	34 (1.6%)	23 (3.5%)	0.0037
SBP (mm Hg)	113.6 ± 11.6	112.8 ± 11.6	113.5 ± 11.6	115.8 ± 11.3	<0.0001
DBP (mm Hg)	75.6 ± 7.8	74.8 ± 7.9	75.8 ± 7.8	77.4 ± 7.4	<0.0001
BMI (kg m^{-2})	24.3 ± 3.0	23.6 ± 2.9	24.5 ± 2.9	25.5 ± 3.1	<0.0001
Triglyceride (mg dl^{-1})	151.8 ± 93.4	142.7 ± 87.8	155.4 ± 94.2	168.9 ± 103.9	<0.0001
HDL-c (mg dl^{-1})	44.8 ± 9.8	45.7 ± 10.1	44.3 ± 9.6	43.2 ± 9.1	<0.0001
Male	*N* = 2,338	*N* = 864	*N* = 1,089	*N* = 385	
Age (years)	50.8 ± 8.4	51.9 ± 8.9	49.9 ± 8.0	50.7 ± 8.0	<0.0001
Regular exercise					
Yes	595 (25.4%)	194 (22.5%)	299 (27.5%)	102 (26.5%)	0.0365
Smoking					
Non-smoker	457 (19.5%)	177 (20.5%)	214 (19.7%)	66 (17.1%)	0.9217
Past-smoker	719 (30.8%)	263 (30.4%)	335 (30.8%)	121 (31.4%)	
Occasional smokers	123 (5.3%)	46 (5.3%)	56 (5.1%)	21 (5.5%)	
Habitual smokers	1,039 (44.4%)	378 (43.8%)	484 (44.4%)	177 (46.0%)	
Drinking					
Non-drinker	468 (20.0%)	188 (21.8%)	202 (18.5%)	78 (20.3%)	0.1625
Past-drinker	239 (10.2%)	99 (11.5%)	106 (9.7%)	34 (8.8%)	
Current drinker	1631 (69.8%)	577 (66.8%)	781 (71.7%)	273 (70.9%)	
HTN family history					
Yes	373 (16.0%)	116 (13.4%)	181 (16.6%)	76 (19.7%)	0.0136
EDS					
ESS > 10	283 (12.1%)	88 (10.2%)	131 (12.0%)	64 (16.6%)	0.0056
DM					

(Continues)

TABLE 1 (Continued)

Variables	Total	Never snorers	Occasional snorers	Habitual snorers	*p*-value
Yes	251 (10.7%)	91 (10.5%)	120 (11.0%)	40 (10.4%)	0.9154
CVD					
Yes	51 (2.2%)	19 (2.2%)	18 (1.7%)	14 (3.6%)	0.0726
SBP (mm Hg)	114.7 ± 10.8	114.8 ± 10.9	114.2 ± 10.8	115.9 ± 10.7	0.0286
DBP (mm Hg)	77.2 ± 7.3	76.8 ± 7.2	77.1 ± 7.4	78.2 ± 7.0	0.0095
BMI (kg m^{-2})	24.0 ± 2.8	23.3 ± 2.7	24.1 ± 2.7	25.1 ± 2.9	<0.0001
Triglyceride (mg dl^{-1})	168.0 ± 104.6	160.9 ± 104.9	169.5 ± 105.8	179.7 ± 99.6	0.0109
HDL-c (mg dl^{-1})	43.4 ± 9.7	44.4 ± 10.3	43.1 ± 9.4	41.8 ± 8.7	<0.0001
Female	*N* = 2,616	*N* = 1,245	*N* = 1,097	*N* = 274	
Age (years)	50.7 ± 8.5	49.9 ± 8.5	50.8 ± 8.4	54.4 ± 8.3	<0.0001
Regular exercise					
Yes	691 (26.4%)	305 (24.5%)	315 (28.7%)	71 (25.9%)	0.0681
Smoking					
Non-smoker	2,511 (96.0%)	1,188 (95.4%)	1,059 (96.5%)	264 (96.4%)	0.7616
Past-smoker	26 (1.0%)	14 (1.1%)	10 (0.9%)	2 (0.7%)	
Occasional smokers	26 (1.0%)	14 (1.1%)	8 (0.7%)	4 (1.5%)	
Habitual smokers	53 (2.0%)	29 (2.3%)	20 (1.8%)	4 (1.5%)	
Drinking					
Non-drinker	1825 (69.8%)	890 (71.5%)	747 (68.1%)	188 (68.6%)	0.2868
Past-drinker	62 (2.4%)	31 (2.5%)	27 (2.5%)	4 (1.5%)	
Current drinker	729 (27.9%)	324 (26.0%)	323 (29.4%)	82 (29.9%)	
HTN family history					
Yes	490 (18.7%)	210 (16.9%)	231 (21.1%)	49 (17.9%)	0.0322
EDS					
ESS > 10	419 (16.0%)	162 (13.0%)	187 (17.0%)	70 (25.5%)	<0.0001
DM					
Yes	186 (7.1%)	63 (5.1%)	79 (7.2%)	44 (16.1%)	<0.0001
CVD					
Yes	41 (1.6%)	16 (1.3%)	16 (1.5%)	9 (3.3%)	0.0507
SBP (mm Hg)	112.5 ± 12.1	111.5 ± 11.8	112.9 ± 12.3	115.7 ± 12.2	<0.0001
DBP (mm Hg)	74.2 ± 8.1	73.4 ± 8.0	74.6 ± 8.1	76.4 ± 7.8	<0.0001
BMI (kg m^{-2})	24.5 ± 3.1	23.9 ± 2.9	24.8 ± 3.0	26.0 ± 3.3	<0.0001
Triglyceride (mg dl^{-1})	137.3 ± 79.3	130.0 ± 71.0	141.5 ± 78.8	153.8 ± 108.0	<0.0001
HDL-c (mg dl^{-1})	46.0 ± 9.7	46.7 ± 9.9	45.5 ± 9.6	45.2 ± 9.3	0.0059

Note. BMI, body mass index; CVD, cardiovascular diseases, including myocardial infarction, congestive heart failure, coronary arterial disease; DBP, diastolic blood pressure; DM, diabetes mellitus; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; HDL-c, high-density lipoprotein cholesterol; HTN, hypertension; SBP, systolic blood pressure.

[a]Mean ± SD.

[b]*n* (%).

of EDS, habitual snorers had significantly increased incidence rates compared with never snorers. No significant differences in the incidence of hypertension were observed in other age groups.

In addition, Table 3 shows the HRs of occasional and habitual snorers with and without EDS, compared with never snorers without EDS. Only habitual snoring was significantly associated with 1.5- and 2.0-fold excess risk for the incidence of hypertension when EDS was absent and present, respectively.

4 | DISCUSSION

This study prospectively observed 4,954 middle-aged and older adults who were free of hypertension at baseline for 14 years. A major finding was that habitual snoring at least 4 nights a week may increase the risk for the development of new-onset hypertension in relatively young male adults (aged 40–45 years), but not in older men. In this age group, habitual snoring was significantly associated

TABLE 2 Univariate and multivariate Cox proportional hazards models of the14-year incidence of hypertension in total participants, and by sex and age groups

			Crude HR		Adjusted HR[a]	
	Frequency of snoring	No. of cases/total	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Total	Never snorers	995/2,109	Reference			
	Occasional snorers	1,109/2,186	1.11 (1.02–1.21)	0.018	1.01 (0.93–1.10)	0.816
	Habitual snorers	374/659	1.32 (1.17–1.48)	<0.001	0.95 (0.84–1.07)	0.413
Age stratification						
40–45 years	Never snorers	240/802	Reference		Reference	
	Occasional snorers	319/819	1.41 (1.19–1.66)	<0.001	1.12 (0.94–1.33)	0.218
	Habitual snorers	90/180	2.01 (1.58–2.57)	<0.001	1.21 (0.94–1.57)	0.140
46–55 years	Never snorers	305/655	Reference		Reference	
	Occasional snorers	382/791	1.07 (0.92–1.24)	0.399	0.95 (0.82–1.11)	0.533
	Habitual snorers	120/240	1.08 (0.88–1.34)	0.455	0.84 (0.67–1.04)	0.106
56–65 years	Never snorers	289/443	Reference		Reference	
	Occasional snorers	259/392	1.02 (0.86–1.20)	0.837	0.99 (0.83–1.17)	0.864
	Habitual snorers	119/174	1.14 (0.92–1.41)	0.236	1.00 (0.80–1.25)	0.988
66 years or older	Never snorers	161/209	Reference		Reference	
	Occasional snorers	149/184	1.04 (0.83–1.30)	0.733	0.95 (0.75–1.19)	0.652
	Habitual snorers	45/65	0.83 (0.59–1.15)	0.254	0.75 (0.53–1.05)	0.094
Male	Never snorers	448/864	Reference		Reference	
	Occasional snorers	584/1,089	1.05 (0.93–1.19)	0.443	1.02 (0.90–1.16)	0.707
	Habitual snorers	218/385	1.13 (0.96–1.33)	0.135	0.95 (0.81–1.12)	0.561
Age stratification						
40–45 years	Never snorers	105/272	Reference		Reference	
	Occasional snorers	191/438	1.23 (0.97–1.56)	0.093	1.14 (0.89–1.45)	0.306
	Habitual snorers	75/129	1.90 (1.41–2.55)	<0.001	1.50 (1.09–2.06)	0.012
46–55 years	Never snorers	141/285	Reference		Reference	
	Occasional snorers	209/389	1.10 (0.89–1.37)	0.363	1.03 (0.83–1.27)	0.820
	Habitual snorers	77/148	1.02 (0.77–1.34)	0.916	0.91 (0.68–1.21)	0.493
56–65 years	Never snorers	126/203	Reference		Reference	
	Occasional snorers	122/178	1.17 (0.91–1.50)	0.213	1.21 (0.94–1.56)	0.148
	Habitual snorers	46/77	1.02 (0.73–1.43)	0.908	1.10 (0.77–1.57)	0.594
66 years or older	Never snorers	76/104	Reference		Reference	
	Occasional snorers	62/84	0.98 (0.70–1.37)	0.897	0.90 (0.63–1.27)	0.541
	Habitual snorers	20/31	0.73 (0.45–1.20)	0.221	0.70 (0.42–1.18)	0.182
Female	Never snorers	547/1,245	Reference		Reference	
	Occasional snorers	525/1,097	1.13 (1.00–1.27)	0.053	0.95 (0.84–1.07)	0.385
	Habitual snorers	156/274	1.48 (1.24–1.76)	<0.001	0.86 (0.71–1.04)	0.115
Age stratification						
40–45 years	Never snorers	136/534	Reference		Reference	
	Occasional snorers	128/381	1.37 (1.08–1.75)	0.011	1.19 (0.93–1.52)	0.169
	Habitual snorers	15/51	1.15 (0.67–1.96)	0.618	0.91 (0.53–1.56)	0.733
46–55 years	Never snorers	164/370	Reference		Reference	
	Occasional snorers	173/402	1.00 (0.81–1.24)	0.991	0.89 (0.72–1.11)	0.303
	Habitual snorers	43/92	1.08 (0.78–1.52)	0.637	0.87 (0.62–1.23)	0.429

(Continues)

TABLE 2 (Continued)

			Crude HR		Adjusted HR[a]	
	Frequency of snoring	No. of cases/total	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
56–65 years	Never snorers	163/240	Reference		Reference	
	Occasional snorers	137/214	0.91 (0.73–1.14)	0.419	0.85 (0.68–1.08)	0.184
	Habitual snorers	73/97	1.23 (0.94–1.63)	0.137	1.00 (0.74–1.35)	0.997
66 years or older	Never snorers	85/105	Reference		Reference	
	Occasional snorers	87/100	1.06 (0.79–1.43)	0.703	1.06 (0.77–1.44)	0.737
	Habitual snorers	25/34	0.92 (0.59–1.44)	0.722	0.88 (0.55–1.42)	0.597

Note. CI, confidence interval; HR, hazard ratio.

[a]Adjusted for age, BMI, sex, drinking and smoking habits, regular exercise, family history of hypertension, triglyceride, HDL cholesterol, and the presence of diabetes and cardiovascular disease.

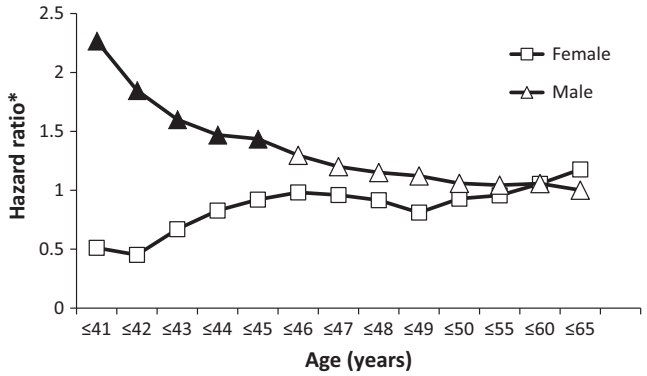

FIGURE 1 Cox hazard ratios (HRs) of habitual snoring for the14-year incidence of hypertension by sex and age.
Note. dark solid marks indicate significant ($p < 0.05$) HRs for the incident hypertension of habitual snoring compared with never-snoring; open marks indicate non-significant HRs. *Adjusted for age, body mass index (BMI), family history of hypertension, smoking, exercise, drinking alcohol, triglyceride, high-density lipoprotein (HDL), and the presence of diabetes and cardiovascular disease

with increased risk for the development of hypertension, regardless of the presence of EDS. The HRs of habitual snoring were highest (HR = 2.5) in 40-year-old men, and gradually decreased with age with no significant differences after age 46 years. In women, snoring did not significantly associate with hypertension incidence in all age groups.

The link between hypertension and snoring has been relatively well established during past decades (Lindberg et al., 1998; Marin et al., 2012), despite some inconsistent findings (Koskenvuo et al., 1994). Physiological mechanisms underlying potential cardiovascular impacts of snoring have been partly explained by oxidative stress, increased inflammatory responses and prolonged sympathetic activation, due to partial or complete obstruction in the upper airway, because habitual snoring is a strong predictor of OSA. In addition, recent studies suggested that transmitted vibration energy induced by snoring may accelerate atherosclerotic responses and endothelial dysfunction in the adjacent vessels and tissues that increase risks for cardiovascular diseases. However, further studies in humans are needed to confirm the independent effects of snoring on cardiovascular diseases, and it still remains unclear if the effect differs by age and sex.

Earlier epidemiological studies reported age-related differences in the association between hypertension and snoring (Koskenvuo, Partinen, & Kaprio, 1985; Lindberg et al., 1998). Lindberg et al. (1998) first reported a possible long-term effect of snoring on the incidence of hypertension. They found that persistent snoring was significantly associated with a higher risk for the development of hypertension over 10 years than never snoring, in all strata of known cardiovascular risk factors such as BMI, smoking, alcohol dependence and physical-activity level; however, the association was not significant in adults aged 50 years and older. This age-dependent association consistently emerged in our previous study (Kim et al., 2007). From a short-term follow-up of the present Korean population-based sample, we found that the association of snoring with the 2-year incidence of hypertension was significant in middle-aged adults only (40–59 years old), not in older adults (≥60 years; Kim et al., 2007). In the present study, we continuously observed the same participants for 14 years, and only male habitual snorers aged 40–45 years had higher risks for future hypertension than their non-snorer counterparts.

Although more evidence is needed to confirm the age-dependent association between snoring and hypertension, some speculations are possible. First, SDB may not worsen over time in older adults. Little information is available on the natural progress of snoring and OSA. However, a large epidemiological study demonstrated that the prevalence of SDB increases until the mid-60s, and diminishes or does not change after age 65 years (Young, Shahar, et al., 2002). Another earlier study suggested that esophageal pressure swings, one of the physiological markers related to adverse cardiovascular outcomes in SDB, decreases with age (Krieger, Sforza, Boudewijns, Zamagni, & Petiau, 1997). Collectively, frequency and severity of SDB may diminish with age; thus, it is conceivable that snoring at a younger age may have greater impacts on cardiovascular alterations than that occurring at an older age. Second, because we were unable to determine the severity of OSA by polysomnography, it is possible that only severe OSA, not mild to moderate OSA or simple snoring, has a significant impact on increasing BP in older adults (Guillot et al., 2013). Third, the effect of SDB may be attenuated by other cardiovascular risk factors that increase with age, such as fat accumulation, abdominal obesity, co-

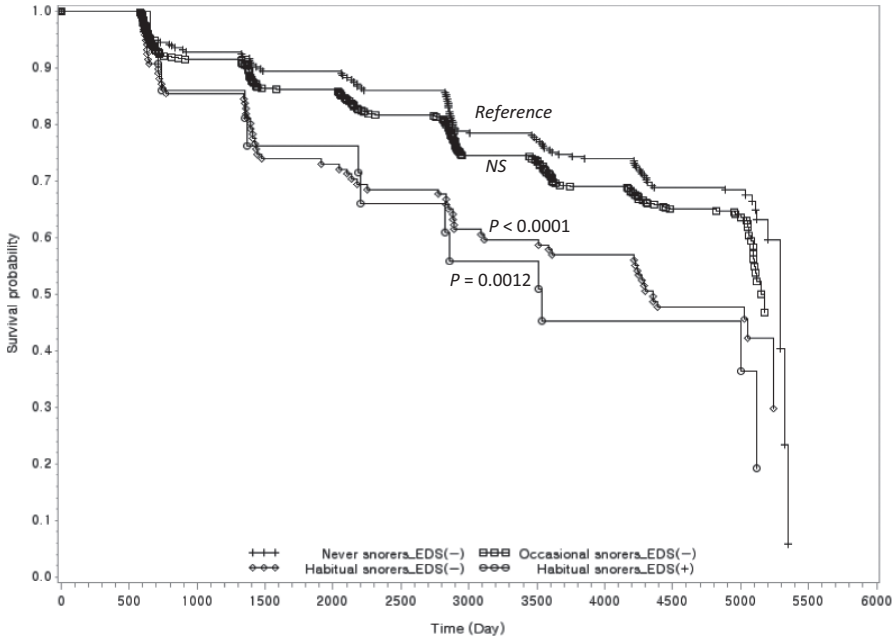

FIGURE 2 Kaplan–Meier survival curves for never snorers, occasional snorers, and habitual snorers with and without excessive daytime sleepiness (EDS) in men aged 40–45 years.
Note. EDS is defined as a total score of Epworth Sleepiness Scale (ESS) greater than 10; NS, non-significant

TABLE 3 Cox HRs of occasional and habitual snorers with and without EDS for the 14-year incidence of hypertension in men aged 40–45 years

Frequency of snoring	HR[a]	95% CI	*p*-value
No EDS (ESS ≤ 10)			
Never snorer	Reference		
Occasional snorer	1.16	0.90–1.51	0.2591
Habitual snorer	1.51	1.07–2.12	0.0183
EDS (ESS > 10)			
Never snorer	1.57	0.87–2.83	0.1331
Occasional snorer	1.45	0.92–2.28	0.1058
Habitual snorer	1.98	1.09–3.62	0.0252

Note. CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; HR, hazard ratio.
[a]Adjusted for age, BMI, family history of hypertension, smoking, exercise, drinking alcohol, triglyceride, HDL, and the presence of diabetes and cardiovascular disease. Regardless of the presence of EDS, habitual snorer was significantly associated with increased risk for incident hypertension.

morbid conditions, and cholesterol and glucose levels. Last, the Sleep Heart Health study recently proposed the possibility that SDB might align with risks for isolated systolic hypertension (ISH), which is more predominantly observed in older adults, rather than the combination of systolic and diastolic hypertension (Haas et al., 2005). We performed a sub-analysis to examine the effect of snoring on the 14-year incidence of ISH in our study sample. However, no significant association emerged in men (HR = 0.88; 95% CI: 0.50–1.56) or women (HR = 0.83; 95% CI: 0.51–1.36).

Whether gender differences exist in the effect of SDB on cardiovascular diseases remains inconclusive. Some previous studies with women demonstrated a significant association between self-reported snoring and cardiovascular outcomes (Hu et al., 1999; Leineweber et al., 2004; Sands et al., 2013), and no gender difference in the link between OSA and hypertension emerged in other studies (Nieto et al., 2000; Peppard et al., 2000). A recent Chinese study compared the presence of hypertension across mild, moderate and severe OSA groups between male and female patients (Yu et al., 2014). The authors found that the proportion of hypertension significantly increased with the severity of OSA in men, but no significant difference emerged in women. In a prospective study in the Victoria Sleep Cohort, sleep apnea aligned with increased risk for Stage 2 hypertension in men, but not in women (Cano-Pumarega et al., 2017).

With regard to gender differences in OSA, prevalence and severity of the disease is much less in women than in men. The male to female ratio of OSA incidence is between 3:1 and 5:1 in general populations (Lin et al., 2008; Young et al., 1993). Using 23,806 patients' data over 10 years, Gabbay and Lavie showed that mean apnea–hypopnea index is significantly lower in women than men in all age groups between 21 and 80 years (Gabbay & Lavie, 2012), consistent with previous studies (O'Connor, Thornley, & Hanly, 2000; Ware, Mcbrayer, & Scott, 2000). In addition to the lower severity of OSA in women than in men, protective effects of the sex hormone progesterone on cardiovascular diseases (Schwertz & Penckofer, 2001) and upper airway patency (Hou et al., 2010) might relate to gender-dependent effects of SDB on hypertension. However, further studies are needed to examine gender difference in characteristics and severity of snoring.

To the best of our knowledge, this study is the longest follow-up study on the association between snoring and the development of hypertension in an Asian population. Despite general consensus on the causal effect of SDB on hypertension, it is still controversial whether this effect is independent of other cardiovascular risk factors, and differs by age, gender and ethnic group. Therefore, the present findings provide valuable information suggesting possible age- and gender-related differences in the effect of snoring on the

development of hypertension. Another strength of this study is that BP measurements and questionnaire surveys on medications and other risk factors have been conducted by well-trained examiners using standardized protocols. Inter-rater reliability of the measurement of BP has been tested every year over the 14 years of the study period.

However, the study has some limitations. First, we used self-reported snoring frequency. Even though we found substantial consistency in the answers to snoring questions through test–retest reliability (kappa value = 0.73), we still cannot rule out the possibility of under- or overestimation of snoring. Second, the present study did not assess the age at which habitual snoring began. Although a significant effect of snoring on hypertension emerged in younger adults in the present study, whether early-onset versus late-onset snoring made a difference in the long-term effects on hypertension and cardiovascular outcomes in the elderly warrants further study. Third, due to the limited age distribution in the present study, ranging between 40 and 69 years at baseline, the potential impact of snoring on hypertension in adults younger than 40 years old could not be assessed. To date, only a few studies investigated whether SDB increases risk for hypertension in a young-adult population, and results are extremely controversial (Asha'ari, Hasmoni, Ab Rahman, Yusof, & Ahmad, 2012; Pensuksan et al., 2014). Last, the diagnosis of hypertension was based on BP measurements from a single visit. This is a critical limitation of a large-scale epidemiological study. However, to minimize possible misdiagnosis, we rigidly followed a standardized protocol employed in other large epidemiological studies (Muntner et al., 2010; Niiranen et al., 2017). All participants took at least a 5-min rest before BP measurement, and we averaged two readings measured at intervals of 30 s.

In conclusion, this study found that habitual male snorers aged between 40 and 45 years are at increased risk for the development of hypertension, independent of other risk factors. The HRs of snoring declined with increased age in men, and no significant association between snoring and hypertension emerged in all age groups in women. This outcome suggests that early detection and treatment of SDB in men may be critical to reduce hypertension incidence and further cardiovascular risks. However, to assert that snoring has larger impacts on cardiovascular alterations at a younger age than at an older age requires further investigation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

SL, JK and CS contributed to the design and implementation of the research; SL and KC analysed the data and wrote the manuscript with input from all authors. All authors discussed the results. JK and YC contributed to the final version of the manuscript.

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