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Self-reported snoring is associated with chronic kidney disease independent of metabolic syndrome in middle-aged and elderly Chinese

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ABSTRACT

Aims/Introduction: To investigate the correlation between snoring and chronic kidney disease (CKD), and explore whether metabolic syndrome (MetS) plays an important role in this relationship among middle-aged and elderly Chinese.

Materials and Methods: The participants included in the present study were categorized into three subgroups based on self-reported snoring frequency (regularly [≥3 times per week], occasionally [between 'regularly' and 'never'] or never [<1 time per month]). An estimated glomerular filtration rate <60 mL/min/1.73 m^2 was considered as CKD. We diagnosed MetS based on the 2004 Chinese Diabetes Society criteria. We explored the relationship between snoring and CKD by using multiple logistic regressions.

Results: The frequency of MetS, MetS components and CKD was dramatically higher in regular snorers than in non-snorers and occasional snorers. The odds ratios for MetS and all the MetS elements, except for hyperglycemia, increased progressively with the snoring frequency ($P < 0.001$). Upon additional adjustment for other MetS components, snoring was not significantly related with hypertension; however, the associations between snoring frequency and overweight/obesity and dyslipidemia became attenuated, but still remained statistically significant ($P < 0.01$). Interestingly, odds ratios for CKD also increasingly augmented with snoring frequency ($P < 0.001$). Upon further adjustment for individual MetS components or MetS, regular snoring also resulted in a significantly increased odds ratio for CKD (odds ratio 1.72; $P = 0.034$) relative to non-snoring.

Conclusions: Self-reported snoring is closely associated with CKD independent of MetS among middle-aged and elderly Chinese.

INTRODUCTION

Chronic kidney disease (CKD) is emerging as one of the biggest global public health issues with rapidly expanding prevalence[1,2]. CKD contributes to the development of cardiovascular events and mortality[3,4]. Metabolic syndrome (MetS), which includes hyperglycemia, hypertension, dyslipidemia and obesity, is a well-known risk factor for CKD[5]. However, these metabolic disturbances do not sufficiently account for CKD progression; thus, novel risk factors for CKD must be identified for use in patient screening.

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Obstructive sleep apnea (OSA), with the characteristic of upper airway obstruction, is the most common sleep problem leading to sleep fragmentation and intermittent hypoxia. OSA is closely related with an increased risk for metabolic disorders, including diabetes and hypertension, which can subsequently facilitate the progression of CKD[6–8]. In addition to indirect effects, a direct effect of OSA on CKD development and progression has been suggested[9]. However, the results are inconsistent, and additional investigation of the association between OSA and CKD is required.

Although snoring is a weakly specific manifestation of OSA, accumulating evidence has shown the association between regular snoring and various metabolic problems, including

hypertension, type 2 diabetes and MetS[10–13], the most common CKD risk factors. Although the relationship between OSA and CKD has been well studied[14], the specific relationship between snoring and CKD remains unclear. In addition, whether snoring is associated with CKD dependently or independently of metabolic disorders also remains unknown. Here, we carried out this cross-sectional study in middle-aged and elderly Chinese populations to address these issues.

METHODS

Ethics statement

The present study was a component of the baseline Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal (REACTION) study, which recruited 259,657 participants (aged ≥40 years) from 25 communities in mainland China during 2011–2012[15]. All of the participants signed informed consent. The Ruijin Hospital ethics committee of the Shanghai Jiao Tong University approved this study.

Study participants

10,028 adults (aged ≥40 years) from Shandong province were randomly recruited during January to April 2012, as described previously[16]. Briefly, the snoring frequency was recorded from the questionnaire 'Did you snore in the last year?', which included three levels (regularly [≥3 times per week], occasionally [between 'regularly' and 'never'] or never [<1 time per month]), and 3,520 participants provided specific answers (6,508 participants did not provide specific answers). Then, the exclusion criteria of this study were as follows: (i) missing data for the estimated glomerular filtration rate (GFR; eGFR) calculations; (ii) missing data for diagnosis of MetS; (iii) previously diagnosed kidney disease, such as autoimmune or drug-related kidney disease, nephritis, renal fibrosis or renal failure; (iv) previously diagnosed hepatic disease, such as fatty liver, liver cirrhosis and autoimmune hepatitis; and (v) any malignant diseases. Ultimately, 3,279 individuals (including 2,057 women) were included for analysis.

Data collection

Demographic and lifestyle information was collected from a standard questionnaire by face-to-face interview. Current smoking status and alcohol intake were reported as binary variables (yes, no). Body mass index (BMI) was defined as weight (kg) divided by squared body height (m^2). Blood pressure was measured for all participants using OMRON Model HEM-752 FUZZY (Omron Company, Dalian, China) from the left arm three consecutive times after they were seated for >5 min. The mean of three readings was used for further statistics. Fasting blood glucose, triglyceride, high-density lipoprotein cholesterol and creatinine were measured with overnight fasting venous blood samples. The 2-h plasma glucose was assayed when the participants underwent a 75-g oral glucose tolerance test. High-performance liquid chromatography (VARIANT II and D-10 Systems; Bio-Rad, Hercules, California, USA) was taken to assay hemoglobin A1c. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on creatinine levels[17]. All relevant data are presented in Supplemental Files-data.xls.

Definitions

eGFR < 60 mL/min/1.73 m^2 was considered as CKD based on the Kidney Disease Outcomes Quality Initiative provided by the USA National Kidney Foundation[18]. Serum creatinine levels were assayed with the picric acid method using the automatic analyzer (ARCHITECT ci16200 Integrated System; Abbott Laboratories, Abbott Park, Illinois, USA) at the standardized laboratory of Ruijin Hospital in Shanghai, China.

According to the Chinese Diabetes Society criteria in 2004[19], MetS was diagnosed when at least three of the following disorders occurred: (i) overweight and/or obesity – BMI ≥ 25.0 kg/m^2; (ii) hyperglycemia – fasting plasma glucose ≥6.1 mmol/L and/or 2-h plasma glucose ≥7.8 mmol/L or diagnosed as type 2 diabetes mellitus before or received medicine; (iii) hypertension – systolic/diastolic blood pressure ≥140/90 mmHg or diagnosed hypertensive before and received medicine; and (iv) dyslipidemia – triglyceride level ≥1.7 mmol/L and/or high-density lipoprotein cholesterol level <0.9 mmol/L (men) or <1.0 mmol/L (women).

Statistical analysis

Continuous variables showing normal distributions were presented as the mean ± standard deviation, whereas variables with non-normal distributions were shown as medians (interquartile range). Values (%) were used to express categorical variables. One-way ANOVA (least significant difference; continuous variables showing normal distributions), the Kruskal–Wallis *H*-test (skewed continuous variables) and χ^2-test (categorical variables) were carried out to compare the differences in the three groups. The relationships between the snoring frequency and MetS, MetS components, and CKD were statistically evaluated by multiple logistic regressions with adjustments of relevant covariates as follows: model 1 was not adjusted; model 2 was adjusted with sex and age; and model 3 was adjusted with age, sex, smoking status and alcohol intake. Subsequent models were further adjusted for different MetS components in addition to the model 3 covariates. The linear trends in the relationship between the snoring frequency and MetS, MetS components, and CKD were calculated by considering the snoring frequency as continuous variables. Statistical significance was defined as $P < 0.05$. All of the statistics were taken by SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Study participant characteristics based on snoring frequency

A total of 3,279 adults including 2,057 women were divided into three groups accorded with the snoring frequency. As

shown in Table 1, the prevalence of MetS and CKD was 34.0 and 4.9%, respectively. Compared with non-snorers and occasional snorers, regular snorers were older, male, smokers and alcohol drinkers. Additionally, regular snorers showed an increased incidence of MetS, MetS components and CKD.

Relationship between snoring frequency and MetS by multiple logistic regression analysis

We next investigated the relationships between the snoring frequency and MetS or each MetS component by using different models. As presented in Table 2, the odds ratios (ORs) of MetS showed a progressive increase along with the snoring frequency ($P < 0.001$), and regular snorers showed an OR of 1.70 ($P < 0.001$) relative to non-snorers with adjustment of age, sex, smoking status and alcohol drinking (model 3). The MetS components showed similar trends, except for hyperglycemia, after adjusting for the aforementioned covariates (model 3). However, when further adjustments for other components in MetS were included (model 4), the associations between snoring frequency overweight/obesity and dyslipidemia were attenuated, but still remained significant ($P < 0.01$). No significant differences were observed in the relationship between snoring frequency and hypertension after these additional adjustments based on model 4.

Relationship between snoring frequency and CKD by multiple logistic regressions analysis

To elucidate the specific relationship between snoring frequency and CKD, and whether MetS plays a role in this relationship, we used different models. As presented in Table 3, the ORs for CKD increased progressively with the snoring frequency ($P < 0.001$), and an OR of 1.79 was shown in regular snorers ($P = 0.022$) relative to non-snorers after adjusting for age, sex, smoking and alcohol drinking (model 3). When we adjusted of MetS components or MetS, regular snorers showed significantly greater ORs for CKD (models 4–8).

DISCUSSION

The main findings of the present study were the close relationships between snoring, a common but weakly specific marker of OSA, and CKD independent of MetS. The associations between sleep disturbances and the development or progression of CKD have recently been well studied[9]. These results are inconsistent; however, it appears that sleep disturbances exert a negative effect on CKD. In addition, polysomnography is the gold standard of evaluating sleeping quality. It combines whole-night recordings with a multiple-lead electroencephalogram of muscle tones or eyes movement measurements; however, polysomnography is too complicated and time-consuming to

Table 1 | Characteristics of the study participants based on snoring frequency

Characteristic	Snoring frequency			*P*-value
	Never *n* = 877	Occasionally *n* = 1,596	Regularly *n* = 806	
Female (%)	614 (70.0)	1,053 (66.0)	390 (48.4)	<0.001
Age (years)	59.33 ± 9.97	58.98 ± 9.62	60.42 ± 8.87	0.002
BMI (kg/m^2)	25.72 ± 3.29	26.26 ± 3.43	27.05 ± 3.51	<0.001
SBP (mmHg)	139.06 ± 20.26	140.02 ± 21.22	142.52 ± 19.26	0.002
DBP (mmHg)	79.65 ± 11.26	79.92 ± 11.47	81.65 ± 11.46	<0.001
FPG (mmol/L)	5.98 ± 1.72	5.98 ± 1.81	6.34 ± 1.90	<0.001
2hPG (mmol/L)	7.30 (4.90–8.00)	7.34 (4.92–8.17)	7.79 (5.00–9.00)	0.002
HbA1c (%)	6.18 ± 1.19	6.17 ± 1.10	6.34 ± 1.19	0.002
TG (mmol/L)	1.51 (0.91–1.79)	1.59 (0.93–1.89)	1.73 (1.06–2.07)	<0.001
HDL-C (mmol/L)	1.50 ± 0.35	1.49 ± 0.32	1.44 ± 0.30	<0.001
eGFR (mL/min/1.73 m^2)	89.79 ± 13.94	88.79 ± 15.03	84.37 ± 14.39	<0.001
Smoking (%)	82 (9.4)	174 (10.9)	156 (19.4)	<0.001
Drinking (%)	62 (7.1)	127 (8.0)	144 (17.9)	<0.001
Overweight/obesity (%)	482 (55.0)	990 (62.0)	580 (72.0)	<0.001
Hyperglycemia (%)	325 (37.1)	574 (36.0)	357 (44.3)	<0.001
Hypertension (%)	497 (56.7)	921 (57.7)	543 (67.4)	<0.001
Dyslipidemia (%)	261 (29.8)	517 (32.4)	326 (40.4)	<0.001
MetS (%)	268 (30.6)	499 (31.3)	347 (43.1)	<0.001
CKD (%)	29 (3.3)	77 (4.8)	54 (6.7)	0.005

Data are expressed as the mean ± standard deviation, median (interquartile range) or *n* (%). 2hPG, 2-h plasma glucose; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; TG, triglyceride.

Table 2 | Multiple logistic regression analysis of the association between snoring frequency and metabolic syndrome

	Never	Occasionally Odds ratio (95% CI), *P*-value	Regularly Odds ratio (95% CI), *P*-value	*P* for trend
MetS				
Model 1	1	1.03 (0.87–1.24), 0.716	1.72 (1.41–2.10), <0.001*	<0.001*
Model 2	1	1.05 (0.88–1.26), 0.579	1.69 (1.38–2.08), <0.001*	<0.001*
Model 3	1	1.05 (0.88–1.26), 0.575	1.70 (1.38–2.09), <0.001*	<0.001*
Overweight/obesity				
Model 1	1	1.34 (1.13–1.58), 0.001*	2.10 (1.72–2.58), <0.001*	<0.001*
Model 2	1	1.34 (1.13–1.58), 0.001*	2.03 (1.65–2.49), <0.001*	<0.001*
Model 3	1	1.34 (1.13–1.58), 0.001*	2.04 (1.66–2.51), <0.001*	<0.001*
Model 4	1	1.34 (1.12–1.59), 0.001	1.84 (1.49–2.28), <0.001	<0.001
Hypertension				
Model 1	1	1.04 (0.88–1.23), 0.618	1.58 (1.29–1.93), <0.001*	<0.001*
Model 2	1	1.05 (0.89–1.25), 0.567	1.42 (1.15–1.74), 0.001*	<0.001*
Model 3	1	1.05 (0.88–1.25), 0.572	1.40 (1.14–1.73), 0.002*	<0.001*
Model 4	1	0.99 (0.83–1.19), 0.926	1.17 (0.94–1.45), 0.157	0.667
Hyperglycemia				
Model 1	1	0.95 (0.80–1.13), 0.589	1.35 (1.11–1.64), 0.003*	0.667
Model 2	1	0.97 (0.81–1.15), 0.697	1.29 (1.06–1.58), 0.013*	0.667
Model 3	1	0.97 (0.81–1.15), 0.706	1.32 (1.08–1.61), 0.008*	0.667
Model 4	1	0.93 (0.78–1.11), 0.400	1.16 (0.94–1.42), 0.168	0.667
Dyslipidemia				
Model 1	1	1.13 (0.95–1.35), 0.177	1.60 (1.31–1.96), <0.001*	<0.001*
Model 2	1	1.14 (0.95–1.36), 0.152	1.62 (1.32–1.99), <0.001*	<0.001*
Model 3	1	1.14 (0.95–1.36), 0.153	1.61 (1.31–1.98), <0.001*	<0.001*
Model 4	1	1.10 (0.91–1.32), 0.316	1.40 (1.13–1.73), 0.002*	<0.001*

*$P < 0.05$. Model 1: not adjusted; model 2: adjusted for age and sex; model 3: adjusted for age, sex, smoking status and drinking status; and model 4: adjusted as described for model 3 in addition to other metabolic syndrome (MetS) components. CI, confidence interval.

Table 3 | Multiple logistic regression analysis of the association between the snoring frequency and chronic kidney disease

	Never	Occasionally Odds ratio (95% CI), *P*-value	Regularly Odds ratio (95% CI), *P*-value	*P* for trend
Model 1	1	1.48 (0.96–2.29), 0.076	2.18 (1.38–3.46), 0.001*	<0.001*
Model 2	1	1.59 (0.99–2.55), 0.053	1.78 (1.08–2.93), 0.023*	<0.001*
Model 3	1	1.59 (0.99–2.54), 0.055	1.79 (1.09–2.94), 0.022*	<0.001*
Model 4	1	1.55 (0.97–2.49), 0.068	1.69 (1.03–2.80), 0.039*	<0.001*
Model 5	1	1.59 (0.99–2.56), 0.054	1.81 (1.10–2.99), 0.020*	<0.001*
Model 6	1	1.59 (0.99–2.55), 0.053	1.78 (1.08–2.93), 0.024*	<0.001*
Model 7	1	1.57 (0.98–2.52), 0.062	1.70 (1.03–2.81), 0.038*	<0.001*
Model 8	1	1.59 (0.99–2.55), 0.056	1.72 (1.04–2.84), 0.034*	<0.001*

*$P < 0.05$. Model 1: not adjusted; model 2: adjusted for age and sex; model 3: adjusted for age, sex, smoking status and drinking status; model 4: adjusted as described for model 3 in addition to overweight/obesity; model 5: adjusted as described for model 3 in addition to hypertension; model 6: adjusted as described for model 3 in addition to hyperglycemia; model 7: adjusted as described for Model 3 in addition to dyslipidemia; and model 8: adjusted as described for model 3 in addition to metabolic syndrome. CI, confidence interval.

be carried out in typical clinical practice. Therefore, wrist actigraphy and several validated questionnaires are used to assess sleep duration and quality; these techniques were used in most studies to investigate the correlations between sleep disturbances and CKD[9]. However, these methods are not easily implemented for disease prevention among the many individuals who might not undergo the examinations described above. As a common manifestation of the sleep disturbance disease, OSA, snoring can be easily monitored and improved for disease prevention. Only a few studies recently analyzed the correlation between breathing disorder during sleep and CKD independent of other disorders, such as diabetes and hypertension[20]. Therefore, we

explored this issue in the present survey and discovered regular snoring was closely related to CKD independent of MetS.

Sleep disorders can indirectly or directly impact CKD. Their indirect impact might be attributed to the following parameters. Hypertension is the most well recognized risk factor contributing to the development or progression of CKD[21]. Given the well-established relationship between snoring and hypertension by previous studies[22–24], whether snoring affects CKD development by promoting hypertension remains unclear. Therefore, we analyzed the correlation between snoring frequency and hypertension and CKD in the present study. Unexpectedly, our data showed that the snoring frequency was not related with hypertension after multiple adjustments (Table 2; model 4). Our finding is in contrast with previous studies, which might be due to the different populations recruited in these studies. Lindberg *et al.*[23] found snoring was a risk factor for the development of hypertension in men aged <50 years, but there was no such relationship detected in men aged ≥50 years. The present study primarily consisted of middle-aged and older individuals (age of regular snorers 60.42 ± 8.87 years), and most of the participants were aged >50 years. Thus, no correlation between snoring frequency and hypertension was found. Furthermore, the close relationship between snoring frequency and CKD was independent of hypertension (Table 3; model 5). Hyperglycemia and, thus, diabetes, is the most well-known risk factor for CKD[25,26]. Additionally, a significant association between snoring and diabetes has been suggested by many studies[13,27,28]. Therefore, we analyzed the effect of snoring on hyperglycemia and further investigated the possible role of hyperglycemia in the relationship between snoring frequency and CKD. Surprisingly, we did not detect a significant association between snoring frequency and hyperglycemia with other MetS components adjustment (Table 2; model 4); this result was similar to the results of a Korean population-based study[29]. Furthermore, snoring resulted in increased ORs of CKD independent of hyperglycemia (Table 3; model 6). Accumulating evidence has shown that obesity is an independent risk factor of CKD, as well as for the progression from CKD to kidney failure and the need for dialysis[30,31]. Positive associations between snoring and abdominal obesity[12,32] and BMI have been observed[33]. As expected, snoring was positively associated with BMI in the present study (Table 2; model 4). However, on further adjustment for overweight/obesity, snoring frequency remained closely associated with CKD (Table 3; model 4).

In addition to the aforementioned metabolic disorders, dyslipidemia is always observed in CKD patients, and thus might facilitate the development of cardiovascular complications and many other complications of CKD[34]. Furthermore, our present study showed that snoring was significantly associated with dyslipidemia (Table 2; model 4), consistent with a previous study[12]. However, snoring remained significantly associated with CKD after adjusting for dyslipidemia (Table 3; model 7). Even upon adjustment for MetS rather than any individual MetS component, snoring resulted in significantly increased ORs for CKD (Table 3; model 8).

All of the data described above showed that snoring is closely associated with MetS, primarily through the associations between snoring and overweight/obesity and dyslipidemia in the present study. In addition, snoring is associated with CKD independent of its indirect effects on MetS. The additional indirect or direct effects of snoring on CKD require further investigation. In fact, the direct impact of sleep disorders on CKD have been supported by two lines of evidence that have been discussed in detail[9]. First, sleep exerts an important effect on the regulation of kidney function; thus, reduced sleep quality and duration might negatively affect kidney function. Second, recent studies suggest that OSA is an independent risk factor for CKD by inducing endothelial injury or vessel stiffness. Therefore, as a common manifestation of OSA, snoring can also directly affect the development and progression to CKD.

Of course, several limitations existed in the present study. First, the study was cross-sectional, so it cannot avoid causality between snoring and CKD. A prospective study is required to analyze the association between snoring and CKD development or progression. Second, the data about snoring frequency was acquired by a self-reported questionnaire rather than a more accurate assay by polysomnography. Furthermore, other characteristics of snoring, such as loud and disturbing noises, were not considered in the present study. Additionally, other symptoms of OSA, such as daytime sleepiness and fatigue, were not considered here. Third, without measuring the urinary protein levels, eGFR based on creatinine levels using the CKD-EPI equation might not accurately reflect kidney function, and thus affect the accurate evaluation of CKD. However, the gold standard to measure GFR (isotope clearance measurement) was too expensive and time-consuming. Thus, the equation based on creatinine to evaluate GFR is logical in epidemiological surveys. Furthermore, the CKD-EPI equation was more accurate as compared with the Modification of Diet in Renal Disease study equation and the Cockcroft–Gault equation[35]. Thus, the CKD-EPI equation might be the optimal method to estimate the GFR in the present study. Fourth, as there is a high prevalence of hypothyroidism in middle-aged and elderly people, especially in women[36,37], further studies are required to test thyroid function and analyze the relationship between snoring and hypothyroidism. Fifth, the quantity of smoking or drinking is the key to its correlation with hypertension, hyperlipidemia, diabetes and so on. The present study could not classify the smoking and drinking state according to quantity. Despite these limitations, our study revealed an association between disordered breathing during sleep, as defined as regular snoring, and CKD.

In conclusion, the present study shows that snoring is closely associated with CKD independent of MetS. Early detection of patients showing habitual/regular snoring and interventions for the associated MetS could have important preventive implications.

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DISCLOSURE

The authors declare no conflict of interest.

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