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Snoring frequency and risk of type 2 diabetes mellitus: a prospective cohort study

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ABSTRACT

Objective To evaluate the association between snoring frequency and type 2 diabetes mellitus (T2DM) according to age and gender in Chinese population.

Design A cohort study was performed in Suzhou site of the China Kadoorie Biobank. Residents who didn't suffer from T2DM at baseline survey (2004–2008) and in half a year after baseline were enrolled in this study and followed cause-specific morbidity until 31 December 2013. All participants were requested to complete a detailed questionnaire and undergo anthropometric measurements. Cox regression models were used to estimate HRs and 95% CIs for the snoring and T2DM association.

Setting Wuzhong district, Suzhou, China.

Participants A total of 49 453 participants (men: 41.8%; mean age: 51.14±10.28 years) were enrolled in this study.

Outcome measures T2DM cases were defined as International Classification of Diseases 10th Revision code of E11 and were identified through disease registries and health insurance databases.

Results During a media of 7.18 years follow-up, 1120 T2DM cases were identified. Higher T2DM incidence was observed in participants with frequent and occasional snoring compared with those without (4.80 and 2.87 vs 2.39 per 1000 person-years). The multivariable-adjusted model found snoring was independently associated with T2DM (HR 1.28, 95% CI 1.20 to 1.38), both in men (HR 1.25, 95% CI 1.10 to 1.41) and women (HR 1.28, 95% CI 1.17 to 1.39). Moreover, a significant multiplicative interaction effect between snoring and age was detected on T2DM risk (p=0.015).

Conclusions Snoring was independently associated with an increased risk of T2DM in Chinese population, both in men and women. Meanwhile, there was an interaction effect between snoring and age on T2DM risk.

Strengths and limitations of this study

- This is a large-scale cohort study that investigates the independent association between snoring frequency and type 2 diabetes mellitus (T2DM) risk in Chinese population.
- This study comes from China Kadoorie Biobank, a well-established prospective cohort that has detailed baseline and integrated follow-up data.
- Our study conducts interaction analyses between snoring and other covariates on T2DM risk.
- The snoring frequency data are self-reported by the participants.
- This study doesn't have obstructive sleep apnea and excessive daytime sleepiness data, which may confuse the correlation between snoring and T2DM.

INTRODUCTION

It is worthwhile to note that the number of patients with diabetes was estimated to rise from 171 million in 2000 to 366 million in 2030 worldwide.[1] In China, the Report on Nutrition and Chronic Diseases of Chinese Residents indicated that the prevalence of diabetes among residents aged ≥18 years was markedly increased from 2.6% in 2002 to 9.7% in 2015. Diabetes is becoming an urgent global problem in the field of public health.

Snoring has long been recognised as a nuisance, not only for bed partners, but also for snorers. Accumulating epidemiology evidences have theorised that snoring might contributes to cardiovascular and cerebrovascular diseases, metabolic syndrome and impaired glucose tolerance.[2–5] However, the association between snoring and type 2 diabetes mellitus (T2DM) was conflicting. Besides, majority of the studies were cross-sectional studies and were performed in the USA and Europe. There has been very rare prospective study performed in China.

We hypothesised that snorer might have an independently higher risk of T2DM. This study aimed to investigate the possible relationship between snoring and T2DM in a Chinese cohort. Moreover, we focused on age and gender which might be confounded the snoring–T2DM association.

METHODS

Participants

Participants in this study came from Suzhou cohort of the China Kadoorie Biobank study, a well-established prospective cohort during 2004–2008 in China where personal

continuous positive airway pressure (CPAP) machine was seldom used, detail described previously.[6–8] 53 260 participants were recruited at the baseline. All participants should satisfy the following criteria: (a) aged 30–79 years, (b) without major disability, (c) not suffered from stroke, transient ischaemic attack or coronary artery disease at baseline and (d) not suffered from diabetes at baseline and in the coming half a year after entering the cohort. Finally, 49 453 participants formed the sample for this study. Each participant was interviewed for a face-to-face baseline survey by trained staff with a standardised electronic questionnaire, including demographic characteristics, behavioural risk factors, general health and family histories. A physical examination was undertaken by trained physicians, and a blood sample was collected.

Assessment of T2DM

Diabetes at baseline was ascertained by either self-report or screen-detected. Screen-detected diabetes was defined with a blood glucose level conforming to any of the following criteria: (a) a fasting blood glucose level ≥7.0 mmol/L; (b) a random blood glucose level ≥11.1 mmol/L with a fasting time <8 hour and (c) a random blood glucose level ≥7.0 mmol/L with a fasting time >8 hour. Participants with non-fasting glucose levels, ≥7.8 and <11.1 mmol/L, were invited to return for a fasting blood glucose test the next day.[9]

The incident T2DM defined as categories E11 of International Classification of Diseases 10th Revision (ICD-10) was collected by linking to disease registries and health insurance databases until 31 December 2013. These databases recorded details of hospitalised episodes including disease characteristics, diagnostic procedures and ICD-10 codes. The results of proactive community cluster screening for diabetes every year were also contained in these databases. Participants failed to be linked would be followed by research staff annually to ascertain their status, including hospital admission, death registration and migration.[7] Only new T2DM cases confirmed by medical records were considered as incident cases.

Assessment of snoring and covariates

Snoring frequency and other covariates were acquired from questionnaire except metabolic equivalent task (MET; hours/day), body mass index (BMI) and waist-hip ratio (WHR). Snoring frequency was ascertained by the following question: 'Do you snore during sleep?' and categorised as 'frequently', 'occasionally' or 'never'. Smoking status was categorised as the following classes: (a) never smoker, (b) occasional smoker, (c) ex-regular smoker: basically not smoking now, but smoke most days or every day ever and (d) current regular smoker: smoke most days or every day now. Alcohol status was categorised as the following classes: (a) never drinker, (b) occasional drinker: drink less than once a week now and ever, (c) ex-regular drinker: basically not drinking now, but drink every week for at least 1 year ever and (d) current regular drinker: drink more than once a week now. MET was calculated on behalf of total physical activity involving work, transportation, housework and non-sedentary recreation. BMI was calculated by dividing weight by height squared. WHR was calculated by dividing waistline by hipline. Educational attainment was classified as (a) no formal school, (b) primary school, (c) middle school and (d) high school and above. Marital status was classified as married or no married including never married, separated, divorced or widowed. Household annual income was divided into <¥20 000, ¥20 000–¥34 999 and ≥¥35 000. Stroke, transient ischaemic attack, coronary artery heart disease and hypertension at baseline were self-reported. Family history of diabetes was defined as participants whose parents, children or siblings had diabetes. Medications for sleep were ascertained by needing to take medications (including herbal and sleep pills) at least once a week during the past month.

Statistical analysis

The continuous and categorical variables were presented as mean±SD and n (%), respectively. Follow-up time was accrued from baseline survey until the date of T2DM diagnosis, death of any cause, loss to follow-up, or 31 December 2013, whichever occurred first. Three cox proportional hazards regression models were established to examine the association between self-reported snoring and T2DM by calculating the HR and 95% CI. Model 1 only included snoring, age and gender. Model 2 adjusted smoking status, alcohol status, MET, WHR, educational attainment, marital status and household annual income based on model 1. Model 3 adjusted hypertension, diabetes family history and medications for sleep on the basis of model 2. Sensitivity analyses were performed by substituting WHR with BMI and body fat percentage (BFP) respectively in model 3. Then, the data were stratified by age and gender, and the cox regression model 3 described above was aligned again. An interaction test was conducted to estimate whether there were interactive variables on T2DM risk.

All analyses were performed using R V.3.4.3 (The R Foundation). A two-sided $p<0.05$ was considered statistically significant.

Patient and public involvement

Patients and the public were involved in the design, data provision, analysis and publication of the study.

RESULTS

The baseline characteristics of the participants categorised by snoring frequency were shown in table 1. The mean age of the participants was 51.14±10.28 years, 41.8% were men. The frequencies of never, occasional and frequent snoring were 46.9%, 24.4% and 28.7%, respectively. Compared with never snoring, snorers were more likely to be aged, current smokers and drinkers, low MET, high WHR, BMI and BFP, suffering from hypertension,

Table 1 Baseline characteristics of the participants according to snoring frequency (%)

	Never (n=23 208)	Occasionally (n=12 047)	Frequently (n=14 198)
Men	7923 (38.3)	5179 (25.0)	7589 (36.7)
Age (years, x±s)	50.07±10.63	50.79±9.90	53.18±9.69
Smoking status			
Never	15 872 (68.4)	7179 (59.6)	7035 (49.5)
Occasional	890 (3.8)	651 (5.4)	804 (5.7)
Ex-regular	919 (4.0)	632 (5.2)	1056 (7.4)
Current regular	5527 (23.8)	3585 (29.8)	5303 (37.4)
Alcohol status			
Never	15 215 (65.6)	6682 (55.5)	7051 (49.7)
Occasional	4415 (19.0)	2957 (24.5)	3420 (24.1)
Ex-regular	378 (1.6)	205 (1.7)	364 (2.6)
Current regular	3200 (13.8)	2203 (18.3)	3363 (23.7)
Educational attainment			
No formal school	7070 (30.5)	3159 (26.2)	4358 (30.7)
Primary school	7336 (31.6)	3687 (30.6)	4965 (35.0)
Middle school	6753 (29.1)	3749 (31.1)	3552 (25.0)
High school and above	2049 (8.8)	1452 (12.1)	1323 (9.3)
Household income (¥)			
<20 000	6230 (26.8)	2755 (22.9)	3947 (27.8)
20 000–34 999	7705 (33.2)	3838 (31.9)	4217 (29.7)
≥35 000	9273 (40/0)	5454 (45.3)	6034 (42.5)
WHR (x±s)	0.87±0.06	0.89±0.07	0.91±0.07
BMI (kg/m^2, x±s)	23.11±2.91	24.18±3.00	25.15±3.33
BFP (%, x±s)	27.59±7.61	28.69±7.91	29.27±8.55
MET (x±s)	26.34±15.14	25.87±14.64	25.72±15.42
Married	21 304 (91.8)	11 359 (94.3)	13 316 (93.8)
Hypertension (yes)	1905 (8.2)	1474 (12.2)	2288 (16.1)
Family history of diabetes (yes)	1207 (5.4)	804 (6.9)	980 (7.1)
Medications for sleep (yes)	326 (1.4)	158 (1.3)	160 (1.1)

BFP, body fat percentage; BMI, body mass index; MET, metabolic equivalent task; WHR, waist-hip ratio.

having family history of diabetes, but not taking medications for sleep.

During a median of 7.18 years and 0.35 million person-years follow-up, 1120 incident cases of T2DM were identified. Higher T2DM incidence was observed in participants with frequent and occasional snoring compared with those without (4.80 and 2.87 vs 2.39 per 1000 person-years, table 2). Table 2 also showed the results of multivariable cox regression models examining the effects of baseline snoring status on the development of T2DM. Co+mpared with those without snoring, the HRs for T2DM adjusted by age and gender were elevated in both occasional and frequent snorers; whereas, the HRs attenuated after adjustment for potential confounders, the snorers were still 1.28 (95% CI 1.20 to 1.38) times more likely to suffer from T2DM than those never snoring in the final model (HR 1.09, 95% CI 0.92 to 1.28 for occasional snorers; HR 1.64, 95% CI 1.42 to 1.88 for frequent snorers). We conducted sensitivity analyses replacing WHR with BMI and BFP, respectively, in model 3. The results remained consistent. Snoring frequency was still associated with T2DM risk (HR 1.13, 95% CI 1.05 to 1.21 for BMI model; HR 1.16, 95% CI 1.08 to 1.25 for BFP model, table 3).

In an effort to investigate the effect of snoring on T2DM risk in the subgroups, we carried out stratification analyses on the variables of age and gender. As shown in table 4, when stratified by age, of interest, a stronger strength of association of snoring with T2DM risk was observed among participants aged >50 years (HR 1.42, 95% CI 1.25 to 1.61), compared with those aged ≤50 years (HR 1.22, 95% CI 1.12 to 1.32) in fully adjusted model (the heterogeneity test p=0.043). When stratified by

Table 2 Adjusted HR (95% CI) for T2DM risk according to snoring

	T2DM cases	Person-years	Model 1*	Model 2†	Model 3‡
Total					
Never snoring	396	165 551.53	1.00	1.00	1.00
Occasional snoring	245	85 252.99	1.22 (1.04 to 1.43)	1.14 (0.97 to 1.34)	1.09 (0.92 to 1.28)
Frequent snoring	479	99 763.91	1.96 (1.71 to 2.24)	1.76 (1.53 to 2.01)	1.64 (1.42 to 1.88)
Overall	1120	350 568.43	1.40 (1.31 to 1.50)	1.33 (1.24 to 1.42)	1.28 (1.20 to 1.38)
Men					
Never snoring	117	54 971.30	1.00	1.00	1.00
Occasional snoring	72	36 074.22	0.95 (0.71 to 1.27)	0.86 (0.63 to 1.16)	0.83 (0.61 to 1.12)
Frequent snoring	198	52 739.19	1.70 (1.35 to 2.13)	1.56 (1.24 to 1.96)	1.48 (1.17 to 1.87)
Overall	387	143 784.71	1.33 (1.18 to 1.49)	1.28 (1.13 to 1.44)	1.25 (1.10 to 1.41)
Women					
Never snoring	279	110 580.23	1.00	1.00	1.00
Occasional snoring	173	49 178.77	1.35 (1.12 to 1.63)	1.29 (1.06 to 1.56)	1.23 (1.01 to 1.49)
Frequent snoring	281	47 024.72	2.07 (1.75 to 2.44)	1.74 (1.47 to 2.06)	1.63 (1.37 to 1.94)
Overall	733	206 783.72	1.44 (1.32 to 1.56)	1.32 (1.21 to 1.44)	1.28 (1.17 to 1.39)

*Model 1 adjusted snoring, age and gender.
†Model 2 adjusted smoking status, alcohol status, MET, WHR, educational attainment, marital status and household annual income based on model 1.
‡Model 3 adjusted hypertension, diabetes family history and medications for sleep based on model 2.
MET, metabolic equivalent task; T2DM, type 2 diabetes mellitus; WHR, waist-hip ratio.

gender, snoring increased 25% (95% CI 1.10 to 1.41) and 28% (95% CI 1.17 to 1.39) T2DM risk in men and women in fully adjusted model, respectively. However, this difference was not statistically significant (the heterogeneity test p=0.776).

Furthermore, we carried out an interaction effect analysis for snoring and age on T2DM risk. As shown in table 5, compared with participants aged ≤50 years without snoring, no significant difference was observed for those aged ≤50 years with occasional snoring, but an increased risk for those aged ≤50 years with frequent snoring. Meanwhile, increased risks were observed in participants aged >50 years without snoring and with occasional snoring, but a similar HR for those aged >50 years with frequent snoring. A significant interaction effect between snoring and age was detected on T2DM risk (p=0.015).

DISCUSSION

Several studies in the past have shown the relationship between snoring and diabetes.[10–12] Most of them were cross-sectional studies, which could hardly draw causal inferences. This study was a prospective cohort study documenting the effects of snoring frequency on T2DM risk in China, where personal CPAP machine was seldom used. This study presented new findings that snoring may have an independent elevated effect on T2DM risk, both in men and women. Meanwhile, snoring and age had an interaction effect on T2DM risk.

Results of this study were consistent with other numerous studies.[10 11] However, a recent meta-analysis consisted of 8 studies pooling 101 246 participants indicates snoring was associated with diabetes in women, but not in men.[12] Another 10-year follow-up study in the municipality of Uppsala, Sweden found habitual snoring

Table 3 Adjusted HR (95% CI) for T2DM risk according to snoring in sensitivity analyses

	T2DM cases	Person-years	HR (95% CI)*	HR (95% CI)†
Never snoring	396	165 551.53	1.00	1.00
Occasional snoring	245	85 252.99	1.00 (0.85 to 1.18)	1.02 (0.87 to 1.21)
Frequent snoring	479	99 763.91	1.26 (1.09 to 1.46)	1.34 (1.16 to 1.55)
Overall	1120	3505 698.43	1.13 (1.05 to 1.21)	1.16 (1.08 to 1.25)

*Sensitivity analysis replacing WHR with BMI in model 3.
†Sensitivity analysis replacing WHR with BFP in model 3.
BFP, body fat percentage; BMI, body mass index; T2DM, type 2 diabetes mellitus; WHR, waist-hip ratio.

Table 4 Stratified analyses of association between snoring and T2DM risk

	T2DM cases*	Person-years*	HR (95% CI)†	P value‡
Age (years)				0.043
≤50	136/73/147	89 735.65/42 091.68/38 551.95	1.42 (1.25 to 1.61)	
>50	260/172/332	75 815.88/43 161.31/61 211.96	1.22 (1.12 to 1.32)	
Gender				0.776
Male	117/72/198	54 971.30/36 074.22/52 739.19	1.25 (1.10 to 1.41)	
Female	279/173/281	110 580.23/49 178.77/47 024.72	1.28 (1.17 to 1.39)	

*Shown by never snoring/occasional snoring/frequent snoring.
†Derived from the model.
‡p values were from the heterogeneity test based on the χ^2-based Q-test.
T2DM, type 2 diabetes mellitus.

was associated with an increased incidence of diabetes in men.[13]Our cohort study found both in men and women there exist the relationship between snoring and diabetes in Chinese population. These inconformity findings may be attributed to difference in ethnicity, study design, sample size, analytic strategy, the definition of snoring and diabetes, etc. Further well-designed researches are warranted to reevaluate the gender differences in the relationship of snoring and T2DM.

As we all know, age is associated with many chronic diseases and other risk factors, such as T2DM and snoring.[14 15] In our study, we conducted a multiplicative interactive analysis for age and snoring on T2DM risk. The result supported an interaction effect on a statistical scale. This finding may indicate that age acts as an effect modifier of snoring in the development of T2DM risk. Although age and snoring increased the risk of T2DM in this study, compared with participants aged ≤50 years without snoring, HR for those participants aged >50 years with frequent snoring was similar to HR for those participants aged ≤50 years with frequent snoring. The combined effect of age and snoring seems weaker than simply additive effect of them. It reminded us that the interaction effects should be considered when exploring the T2DM risk factors.

Several epidemiology studies showed BMI, WHR and BFP were associated with snoring and T2DM.[16–18] In our database, we have three obesity indexes: BMI, WHR and BFP, which were related to each other (BMI and WHR: r=0.58, $p<2.2\times10^{-16}$, BMI and BFP: r=0.69, $p<2.2\times10^{-16}$, WHR and BFP: r=0.30, $p<2.2\times10^{-16}$). To prevent collinearity from affecting the results of the cox models, we chose WHR, which reflected abdominal obesity, as a covariate in our models. For any given BMI and BFP, body fat distribution can vary substantially: some individuals store more fat around their visceral organs (abdominal adiposity) than on their thighs and hip.[17] From the clinical perspective, visceral adipose tissue was known to generate diabetogenic substances.[19] Meanwhile, we also conducted sensitivity analyses substituting WHR with BMI and BFP respectively. The results supported the same conclusion.

Table 5 Interaction between snoring and age on T2DM risk

Age (years)	Snoring	HR (95% CI)	P value
≤50	Never	1.00	
≤50	Occasional	1.10 (0.83 to 1.47)	0.500
≤50	Frequent	2.13 (1.67 to 2.70)	5.89×10^{-10}
>50	Never	1.43 (1.14 to 1.79)	2.10×10^{-3}
>50	Occasional	1.53 (1.20 to 1.96)	6.06×10^{-4}
>50	Frequent	2.09 (1.68 to 2.61)	5.63×10^{-11}
Multiplicative interaction			0.015

T2DM, type 2 diabetes mellitus.

Although the specific pathophysiologic mechanism of the association between snoring and T2DM is still not illuminated, some biological causes have been suggested. Intermittent hypoxia and hypercapnia caused by snoring-induced upper airway obstruction may stimulate the sympathetic nervousness and hypothalamic–pituitary–adrenal axis, then increase the catecholamine and cortisol levels, respectively, thereby cause glucose intolerance and insulin resistance leading to T2DM.[20–22] Hypoxia could also increase the levels of counter-regulatory hormones, and activate proinflammatory cytokines, which may mediate peripheral insulin resistance and induce diabetes.[23–25] In addition, the close relationships between snoring and both subclinical atherosclerosis and cardiovascular disease may trigger the development of diabetes.[26]

Although this cohort study was based on a large sample size and suggested a robust causal association when adjusting various covariates, we still recognised several limitations. First, self-reported data existed recall bias and some participants may not be aware of their snoring status, resulting in misclassification bias. Second, we adopted self-reported snoring frequency but not precise clinical measures like polysomnography, which could result in statistical error. Although precise clinical measures could reduce the error in the analysis, it was unavailable for such a large epidemiological study. Third, during literature

review research, we found snoring was a major symptom of obstructive sleep apnea,[27 28] and it was associated with excessive daytime sleepiness.[29] Both of them may confuse the correlation between snoring and T2DM. However, our database didn't include these two variables.

Despite these limitations, our finding is valuable in that it increases our understanding of the association between snoring and T2DM risk with age considered. Snoring might help doctors to identify individuals at a high risk of T2DM, and propose public health implications for diabetes management. Therefore, more prospective researches are needed to confirm the relationship between snoring and T2DM comprehensively.

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Contributors ZC and LL: designed the CKB study. YH, YG and ZB: collected and collated data of this study. ND and QS: proposed hypothesis and made statistical analysis. YL and MW: provided much advice and directions in both study design and preparing of the manuscript. All the authors have read and approved the final submitted version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained from the Ethics Review Committee of the Chinese Center for Disease Control and Prevention, Beijing, China (no. 005/2004) and Oxford Tropical Research Ethics Committee, University of Oxford, Oxford, UK (no. 025-04).

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