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Original Research

Assessing Whether the Association Between Sleep Apnea and Diabetes is Bidirectional

Chia-Lin Liu MD, MSc [a], Chi-Shin Wu MD, PhD [b,c,*]

[a] Department of Family Medicine, En Chu Kong Hospital, New Taipei City, Taiwan
[b] Department of Psychiatry, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan

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ABSTRACT

Objectives: To determine whether there is a bidirectional association between sleep apnea and diabetes mellitus.
Methods: We conducted longitudinal analyses of a population-based cohort over 12 years using Taiwan's national universal health insurance database. In analysis I, we included 102 355 individuals without type 2 diabetes mellitus at baseline and estimated the hazard ratio of incident diagnosis of type 2 diabetes mellitus for patients with and those without sleep apnea. In analysis II, we included 258 053 participants without sleep apnea at baseline and calculated the hazard ratio of developing sleep apnea for patients with and those without type 2 diabetes.
Results: In analysis I, the incidence rates of type 2 diabetes were 17.7 and 11.1 per 1000 person-years for patients with and those without sleep apnea, respectively. Patients with sleep apnea had an increased risk for diabetes (adjusted hazard ratio [aHR] = 1.33; 95% confidence interval [CI], 1.22 to 1.46). In analysis II, the risk for sleep apnea with diabetes was not statistically significant (aHR = 1.06; 95% CI, 0.98 to 1.16). These associations in both analyses did not substantively change after accounting for various latent periods.
Conclusions: Baseline sleep apnea is associated with incident type 2 diabetes; however, the presence of type 2 diabetes cannot predict the development of sleep apnea.

Mots clés :
association bidirectionnelle
étude longitudinale
apnée du sommeil
diabète sucré de type 2

RÉSUMÉ

Objectifs : Déterminer s'il existe une association bidirectionnelle entre l'apnée du sommeil et le diabète sucré.
Méthodes : Nous avons mené des analyses longitudinales d'une cohorte en population durant 12 ans à l'aide de la banque de données du Taiwan's National Health Insurance, un système de couverture universelle des soins de santé. Dans l'analyse I, nous avons inclus 102 355 individus ne souffrant pas initialement du diabète sucré de type 2 et estimé le rapport de risque de nouveaux diagnostics du diabète sucré de type 2 chez les patients souffrant d'apnée du sommeil et chez ceux n'en souffrant pas. Dans l'analyse II, nous avons inclus 258 053 participants ne souffrant pas initialement d'apnée du sommeil et calculé le rapport de risque de développer l'apnée du sommeil chez les patients souffrant du diabète de type 2 et chez ceux n'en souffrant pas.
Résultats : Dans l'analyse I, les taux d'incidence du diabète de type 2 étaient respectivement de 17,7 et de 11,1 par 1000 personnes-années chez les patients souffrant d'apnée du sommeil et chez ceux n'en souffrant pas. Les patients souffrant d'apnée du sommeil avaient un risque accru de diabète (rapport de risque ajusté [RRa]=1,33; intervalle de confiance [IC] à 95 %, 1,22 à 1,46). Dans l'analyse II, le risque de souffrir d'apnée du sommeil lors de diabète n'était pas statistiquement significatif (RRa=1,06; IC à 95 %, 0,98 à 1,16). Dans les deux analyses, ces associations n'ont pas considérablement changé après avoir pris en considération plusieurs périodes latentes.
Conclusions : La présence initiale de l'apnée du sommeil est associée à l'incidence du diabète de type 2. Cependant, la présence du diabète de type 2 ne pas prédire le développement de l'apnée du sommeil.

* Address for correspondence: Chi-Shin Wu, MD, PhD, Department of Psychiatry, National Taiwan University Hospital and College of Medicine, National Taiwan University, No. 7, Chung-Shan South Road, Taipei 10002, Taiwan.
E-mail address: chishinwu@ntu.edu.tw

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Introduction

Epidemiologic studies have demonstrated an association between sleep apnea and type 2 diabetes mellitus. The relationship between these 2 disorders might be bidirectional (1). Although the association between sleep apnea and diabetes has been shown in several cross-sectional studies (2–5), only a few longitudinal studies have demonstrated a clear temporal relationship between sleep apnea and the onset of diabetes (2,6–12). However, these studies have several limitations, such as small sample size and short follow-up duration; hence, their findings are inconsistent (2,6–12).

In the other direction, it remains unclear whether diabetes is an independent risk factor for sleep apnea. A previous study suggested that patients with diabetes may develop complications with peripheral and autonomic neuropathy and impaired protective reflexes of the upper airway, which ultimately cause sleep apnea (1). Although cross-sectional studies have reported a high prevalence of sleep apnea in patients with diabetes (13–15), no longitudinal study has demonstrated a clear temporal relationship between diabetes and the development of sleep apnea. Furthermore, the onset of both sleep apnea and diabetes mellitus is insidious. If the latent period is not considered, the results would be biased and lead to reverse causality (16,17).

The pathogenesis of diabetes mellitus might be different in Asian populations. Asians have a strong genetic predisposition for type 2 diabetes mellitus and are vulnerable to potential risk factors (18). However, the magnitude of the relationship between body mass index and diabetes in Asians is lower than that in Caucasians (19). The association between sleep apnea and diabetes in East Asian populations is rarely explored.

In this study, we determined whether there is a bidirectional association between sleep apnea and diabetes mellitus by using Taiwan's National Health Insurance claims database. We incorporated various lag times to address the problem of potential reverse causality (20). Furthermore, such associations were explored in differing age groups and genders and according to the presence of metabolic risk factors.

Methods

Data source and study population

This retrospective cohort study utilized data from Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD was created using data regarding the reimbursement claims of Taiwan's National Health Insurance program, which included 22.6 million Taiwanese people in 2007 (98% of the population). The NHIRD contains data regarding beneficiaries' demographic characteristics, clinical diagnoses, prescriptions, hospitalizations and medical expenditures. Information that could be used to identify beneficiaries and medical care providers was anonymized. The database has been used for research regarding several diseases, including type 2 diabetes mellitus and sleep apnea (21–24). This study used the Longitudinal Health Insurance Database (LHID) of 2005, which is a representative subset of the original NHIRD and includes a total of 1 000 000 individuals randomly selected from the NHI Registry for Beneficiaries of 2005. The proposal was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital.

Assessment of sleep apnea and type 2 diabetes mellitus

The validation of the diagnoses of sleep apnea and type 2 diabetes has been documented in previous studies (22–25). In brief, 3766 patients with recorded diagnoses of sleep apnea (International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Clinical Modification [ICD-9-CM] codes 780.51, 780.53 or 780.57) were reviewed; approximately 83% of the patients underwent overnight polysomnography. Of them, 87% were diagnosed with obstructive sleep apnea, and <1% were diagnosed with pure central sleep apnea (22). In addition, 1 study used a questionnaire to assess the accuracy of type 2 diabetes mellitus in the NHIRD. Using this algorithm to define type 2 diabetes mellitus, any inpatient diagnosis or at least 3 outpatient diagnoses within 1 year (ICD-9-CM codes 250.x; except 250.x1 and 250.x3), the sensitivity and positive predictive value were reported to be 96.9% and 93.9%, respectively (23).

Covariates

Several potential confounders might be associated with both sleep apnea and diabetes. Obesity is a shared risk factor for these 2 conditions; however, body mass index data were not available in the NHIRD. Therefore, we used obesity-related cardiometabolic variables (hypertension, hyperlipidemia, congestive heart failure, cerebrovascular disease or use of cardiometabolic agents, including beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or lipid-lowering agents) as proxy measures. In addition, diabetes is highly prevalent in patients with psychiatric illness. Sleep disturbance is a common symptom of psychiatric disorders. Thus, we included psychiatric illness (alcohol use disorder, schizophrenia-spectrum disorders, mood disorders and anxiety disorders) and the use of psychotropic agents (antipsychotics, antidepressants and benzodiazepine) as covariates. Furthermore, we assessed patients' chronic comorbid conditions, including chronic kidney disease, chronic pulmonary disease and chronic liver disease. To control for a potential detection bias, we measured the health system utilization using the number of outpatient visits and histories of hospitalization in the year before the cohort entry date; a detection bias is introduced when patients with 1 disease are more likely to receive medical examinations, thereby increasing the chances of diagnoses of another disease.

Statistical analysis

This study aimed to examine the bidirectional associations between sleep apnea and diabetes mellitus; therefore, we used different study populations and described the sample and analytic procedures separately.

Sleep apnea and incident diabetes (analysis I)

In analysis I, we identified patients diagnosed with sleep apnea between 2000 and 2011. The cohort entry date was defined as the date the first time sleep apnea was diagnosed for each patient. Initially, 11 559 patients with sleep apnea were identified. Patients diagnosed with diabetes before the diagnosis of sleep apnea (n=1590) and patients aged younger than 18 years (n=795) were excluded. Finally, 9174 patients with sleep apnea were enrolled in the analysis. For each patient with sleep apnea, we randomly selected 10 comparison subjects who did not have sleep apnea and who were individually matched by gender and year of birth (Figure A1). The cohort entry date of each comparison subject was equal to the date of his or her matched case. The criterion for comparison subjects was no prior history of diabetes before the cohort entry date. All subjects were followed-up until the diagnosis of diabetes, the end of the study period or the date of withdrawal from the national insurance program, whichever occurred first. The incidence rate of diabetes and the corresponding 95% confidence interval (CI) were calculated based on the Poisson distribution. To estimate the effect of sleep apnea on incident diabetes, we used Cox proportional hazards regression models with adjustment for all the