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Original Article

Nonapnea sleep disorders are associated with subsequent ischemic stroke risk: a nationwide, population-based, retrospective cohort study

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ABSTRACT

Background and objectives: Obstructive sleep apnea (OSA) is related to an increased risk for stroke and cardiovascular disease. However, studies investigating the relationship between nonapnea sleep disorders (NSD) and the risk for subsequent ischemic stroke are scant. The objective of our study was to assess the association between NSD and the risk for acute ischemic stroke among patients in Taiwan.

Methods: We conducted our longitudinal nationwide, population-based, retrospective study using Taiwan's National Health Insurance Research Database (NHIRD) from January 1997 to December 2001. All study participants were followed until the incidence of ischemic stroke, or until censoring due to death; until withdrawal from the insurance program; or until they were lost to follow-up by the end of 2010. Cox proportional hazard regression analysis was used to assess the association between NSD and subsequent ischemic stroke risk.

Results: We analyzed the data collected from 94,160 participants as a comparison cohort and 47,080 participants as a NSD cohort with the diagnosis date as the index date. The age range of cohorts was 20.0–101.7 years and 64% were women. The average follow-up duration was 9.61 years for the NSD cohort and 9.42 years for the reference cohort. Overall, the ischemic stroke incidence was 1.48-fold higher in the NSD cohort than in the reference cohort (8.87 vs 6.00/1000 individual-years), with an adjusted hazard ratio (HR) of 1.19 after controlling for age, sex, and comorbidities. Our study also showed a 1.35-fold significantly higher risk for developing ischemic stroke in men compared to women. The adjusted HR was 31.2 for elderly patients compared with participants aged ⩽35 years.

Conclusions: Our nationwide, population-based, retrospective cohort study provides evidence that patients with NSD were at increased risk for developing ischemic stroke compared to patients without diagnosed sleep disorder, with men and the elderly being at greatest risk.

1. Introduction

Stroke results in a sudden loss of neurologic function caused by disrupting the blood flow to the brain and is the leading cause of death globally [1,2]. In Taiwan, the major type of stroke is ischemic stroke [2,3], which is similar to that in the rest of the world. Stroke also is a leading cause of disability in adults [4]. Identification of risk factors for stroke is important for the primary and secondary prevention of stroke.

Sleep disorders constitute some of the most unrecognized modifiable risk factors for stroke [5,6]. The field of sleep disorders has strongly focused on obstructive sleep apnea (OSA), which relates to an increased risk for stroke and cardiovascular disease (CVD). OSA is a treatable form of sleep-disordered breathing, in which the upper airway repeatedly closes during sleep. OSA remarkable

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increases the risk for stroke or death from any cause, and the increase is independent of other risk factors including hypertension [7]. Several studies have shown a prevalence of OSA among patients with stroke that exceeds 60% [8–11], compared with 4% in the middle-aged adult population [12].

However, studies investigating the involvement of nonapnea sleep disorder (NSD) in increasing subsequent ischemic stroke risk are scant. Of the studies conducted thus far, habitual sleep patterns have never been found to be important neurobehavioral determinants in the risk for ischemic stroke in postmenopausal women [13]. A meta-analysis of 15 prospective population-based studies showed that short sleep duration ($\leqslant$6 h/night) and long sleep duration ($\geqslant$9 h/night) are predictors of ischemic stroke [14]. Identifying and describing the relationship of NSD and stroke is paramount in the primary and secondary prevention of stroke. The objective of our nationwide, population-based, retrospective cohort study was to assess the association between NSD and the risk for acute ischemic stroke in Taiwan. We hypothesized that NSD was associated with the development of acute ischemic stroke. The study data were derived from Taiwan's National Health Insurance Research Database (NHIRD).

2. Materials and methods

2.1. Data sources

Taiwan launched a single-payer National Health Insurance program on March 1, 1995. Virtually, the entire Taiwanese population (23 million individuals) is enrolled in this program. The database of this program, the NHIRD, contains registration files and original claim data for reimbursement. Large computerized databases derived from this system (http://nhird.nhri.org.tw/en/index.htm) are provided to scientists in Taiwan for research purposes. From the original dataset of 23 million individuals, we randomly selected 1 million individuals with an identical sex and age distribution in relation to the entire Taiwanese population [15]. The data were retrospectively collected from 1996 to 2010 and included the registry of medical facilities, details of inpatients' orders, ambulatory care, dental services, and prescriptions. The data files can be linked to scrambled identification to protect individual privacy. Previous studies showed the accuracy and high validity of diagnoses in the NHIRD [16,17]. The International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) was used to identify the diagnosis of disease. The study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012).

2.2. Study participants

In our longitudinal cohort study, we selected patients with newly diagnosed NSD (ICD-9-CM codes, 307.4 and 780.5), except for sleep apnea syndrome (ICD-9-CM codes, 780.51, 780.53, and 780.57) between January 1, 1997 and December 31, 2001. We excluded patients who had any type of stroke (ICD-9-CM codes, 430–438) before the index date. We conducted a systematic random sampling design to select a comparison cohort from rest of the insured population that was free from sleep disorders and stroke and that was frequency matched by age (every 5 years), sex, and the year of the index date. The comparison to case ratio was 2 to 1. Fig. 1 displays a flowchart diagram explaining the numbers of individuals at each stage of the study.

2.3. Outcome definition

Using the National Health Insurance inpatients files, we selected the study participants who were diagnosed with ischemic stroke (ICD-9-CM codes, 433–438) from January 1, 1997 to December 31, 2010. All study participants were followed up to measure the incidence of ischemic stroke until December 31st, 2010, or until being censored due to death; until withdrawal from the insurance program; or until they were lost to follow-up. Moreover, the baseline comorbidity history for each participant was identified, including hypertension (ICD-9-CM codes, 401–405), diabetes mellitus (DM) (ICD-9-CM code, 250), coronary artery disease (CAD) (ICD-9-CM codes 410–414), congestive heart failure (CHF) (ICD-9-CM codes, 398.91, 402, 404.01, 404.03, 404.10, 404.11, 404.13, and 404.9), peripheral arterial disease (PAD) (ICD-9-CM codes, 440.2, 440.3,

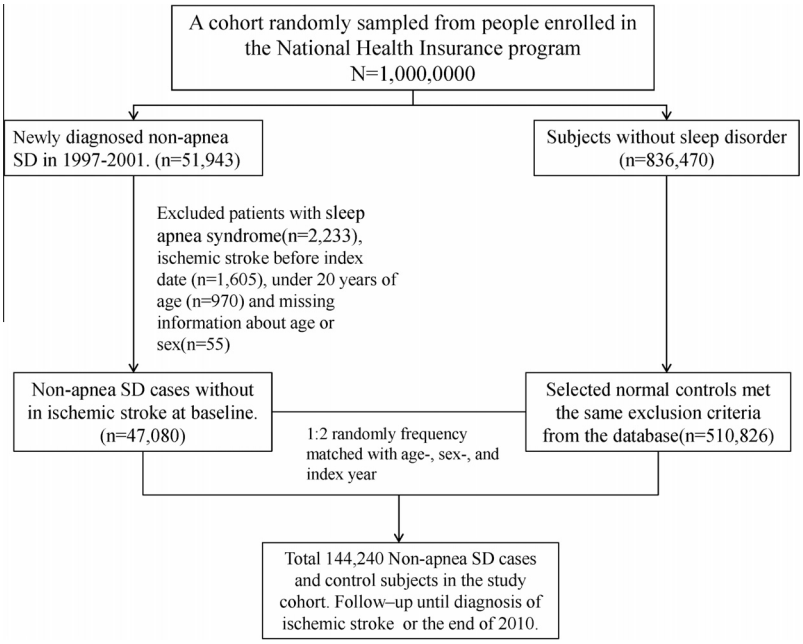

Fig. 1. Study flowchart showing the selection of participants.