INTRODUCTION

Obstructive sleep apnea (OSA), a common disease worldwide, is characterized by repetitive upper airway collapse during sleep, which induces frequent arousal and oxygen desaturation. Using an apnea-hypopnea index (AHI) of 15 as a diagnostic criteria, the prevalence of OSA in the general adult population was found to range from 6% to 17% and can be as high as 49% with advanced age. Obstructive sleep apnea is associated with a range of symptoms, such as fatigue, anxiety, or daytime somnolence. It causes serious complications and increases mortality.

The possibility that OSA is associated depression has been extensively assessed. However, causality in OSA-associated depression is still ambiguous because OSA and depression have similar symptoms and frequently coexist. Recently, a new theory suggests that biological, metabolic, and neurological dysregulation in patients with OSA contributes to the occurrence of depression. In addition, several studies have shown that continuous positive airway pressure (CPAP) therapy in patients with OSA improved depression. However, these findings are often conflicting, and in most studies the results could not be confirmed due to limited population samples. Moreover, the impact of surgical treatment for OSA on depression has not been fully assessed.

The most commonly performed surgical procedure for OSA is uvulopalatopharyngoplasty (UPPP). The success rate of UPPP based on AHI reduction is not high. However, UPPP is an important therapeutic option in patients refusing or intolerant of CPAP. Therefore, it is important to evaluate UPPP not only in terms of AHI reduction but also according to its clinical impact, for example, a reduction in the incidence of depression. However, there are significant difficulties in conducting long-term observational studies of large populations, which explains the limited evidence on patients undergoing UPPP. The National Health Insurance Service (NHIS) database has recently become available for research purposes in Korea and provides large-scale follow-up data on patients with OSA undergoing UPPP. The purpose of this study was to investigate, using NHIS data, whether the incidence of depression increases among patients with OSA and whether UPPP can prevent such an increase.

MATERIALS AND METHODS

Data Source

The NHIS is a national insurer managed by the Korean government, which covers 97% of the Korean population. Both outpatient and inpatient claims are reviewed by the NHIS, and these include data on diagnoses, procedures, prescription

Objective: To investigate the increase in the incidence of depression in patients with obstructive sleep apnea (OSA) and its preventability by uvulopalatopharyngoplasty (UPPP).

Methods: In this retrospective cohort study, data from the Korea National Health Insurance Corporation were analyzed. A total of 160,840 participants (age ≥ 20 years) who were newly diagnosed with OSA between 2007 and 2014 were included. The participants were classified into a group that underwent UPPP (UPPP group, n = 19,773) and a group that did not undergo surgical treatment (no surgery group, n = 141,067). Propensity score matching by age and sex was used to select the control group of 804,200 subjects. The mean follow-up duration was 4.6 ± 2.3 years. The primary endpoint was newly diagnosed depression.

Results: The incidence of depression was higher in patients with OSA than in controls (hazard ratio [HR]: 1.678, 95% confidence interval [CI]: 1.650–1.706). The UPPP group was still at a higher risk of depression than was the control group (HR: 1.535, 95% CI: 1.463–1.610), but the HR was statistically lower than that in the no surgery group (HR: 1.694, 95% CI: 1.665–1.724).

Conclusion: OSA increases the incidence of depression, which may be prevented to some extent by UPPP.

Key Words: Obstructive sleep apnea, depression, uvulopalatopharyngoplasty.

Level of Evidence: 2b

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records, demographic information, and direct medical costs. The NHIS also reviews claims from the Medical Assistance Program and Medical Care for Patriots and Veterans Affairs Scheme, which cover the medical expenses of the Korean population not insured by the NHIS. Therefore, the NHIS database covers the entire Korean population and contains information regarding all medical claims made in Korea. The NHIS identifies its members by their Korean resident registration number, which eliminates the risk of duplication or omission when accessing the data. The NHIS database manages claims using the Korean Classification of Disease, 6th edition, a modified version of the International Classification of Diseases, 10th edition (ICD-10), adapted for the Korean healthcare system. Furthermore, a biennial standardized checkup is recommended for NHIS subscribers. Any researcher can use the NHIS data if the study protocols are approved by the official review committee.

Study Population and Design
We defined the OSA group as including subjects aged ≥20 years with newly diagnosed OSA (G4730) between 2007 and 2014. To select the control group, which was five times larger than the OSA group, propensity score matching by age and sex was used among those who were not diagnosed with OSA. The OSA group was further divided into two groups: 1) the UPPP group comprising patients who underwent UPPP (Q2196 or Q2197), and 2) and the no surgery group comprising subjects who did not undergo surgery. The primary endpoint of this study was newly diagnosed depression (F32 and F33), which was defined using the insurance claims data (Table I). Patients who were diagnosed with depression before enrollment were excluded.

Data Collection
We collected the following baseline data from the NHIS database: age (years), sex, residency (rural or urban), and income level (lowest quintile or the remaining quintiles). Data on comorbidities, including diabetes, hypertension, and dyslipidemia, were also collected using the insurance claims data (Table I).

Statistical Analyses
Data are presented as mean ± standard deviation for age and as proportions for the remaining categorical variables. The Kaplan-Meier plot without covariance correction was presented to analyze the risk of depression according to the presence or absence of OSA and whether the patient underwent UPPP. The incidence rate of depression was calculated by dividing the number of events by the person-time at risk. To determine the hazard ratio (HR) of OSA on the incidence of depression, the Cox proportional hazards model was used after stratifying for covariates, including age, sex, income level, diabetes, hypertension, and dyslipidemia. Two models were used: Model 1 was adjusted by age and sex. Model 2, which was based on model 1, was additionally adjusted for income level, diabetes, hypertension, and dyslipidemia. Finally, the HR for the OSA group was further analyzed by sex, age, diabetes, hypertension, and dyslipidemia. The results are presented as mean and 95% confidence interval. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical Approval
This study involved routinely collected data; therefore, informed consent was not specifically obtained. The study was exempted by the institutional review board of Konkuk University Hospital, Seoul, Republic of Korea due to the use of publicly available data (KUH1110066).

RESULTS
Between 2007 and 2014, there were 160,840 patients newly diagnosed with OSA. Among these, 19,773 underwent UPPP. A total of 804,200 subjects were selected as controls (Fig. 1). Demographic data are summarized in Table II.

Effect of OSA on Incidence of Depression
Depression occurred more frequently in the OSA group than in the control group; this finding was significant in both model 1 and 2. When the OSA group was...
further analyzed, the incidence of depression remained high among both UPPP and no surgery groups in either model 1 or 2. However, the incidence was statistically higher in the no surgery group than the UPPP group. The Kaplan-Meier plot also showed that depression occurred more frequently in the OSA group than in the control group, and that it occurred less frequently in the UPPP group than in the no surgery group (Fig. 2). These results are summarized in Table III.

**Incidence of Depression Among Patients With OSA According to Different Covariates**

Differences in the HR of depression among patients with OSA were observed according to various covariates. Compared with controls with the same condition, the HR values were lower for men; those aged ≥ 40 years; and those with diabetes, hypertension, and hyperlipidemia. The HR difference between the UPPP and no surgery groups was different according to covariates. Compared with controls with the same condition, the difference were greater for women, those younger than 40 years, and those without hypertension and hyperlipidemia. The results of covariate analysis are presented in Table IV.

**DISCUSSION**

Depression is a state of low mood and aversion to activity that can affect a person’s thoughts, behavior, feelings, and sense of well-being. Patients with depression may complain of insomnia, excessive sleeping, and fatigue; and they may report general aches, pains, or...
digestive problems. There are several subtypes of depression, such as persistent depressive disorder, perinatal depression, psychotic depression, seasonal affective disorder, or bipolar disorder. Depression interferes with normal social life, results in decreased productivity, leads to various chronic diseases as well as alcoholism or drug abuse, and even increases suicide rates. Moreover, depression has a very high prevalence, with lifetime prevalence in Western countries ranging from 12.8% to 16.2%, and 1-year prevalence ranges from 3.9% to 6.6%. In Asia, the prevalence is known to be relatively lower than that in Western countries, albeit still high. For example, in Korea, the point prevalence of all types of depression is 6.7%, and major depressive disorder is 2.7%. Due to the serious consequences and high prevalence, depression requires active coping of the whole society.

There have been many studies on the relationship between OSA and depression after it was first reported 30 years ago. Ten years after this initial report, a depressive mood was formally considered one of the symptoms of OSA. The rate of depression among OSA patients ranges from 17% to 41%. Some studies have shown that OSA also occurs frequently among patients with depression. Many studies have reported that the various symptoms that OSA patients complain about are actually related to depression. The most typical symptom of OSA, daytime drowsiness, was reported to be more closely related to the presence or absence of depressive mood rather than the degree of OSA based on the AHI. In addition, the quality of life felt by OSA patients was not associated with the AHI or oxygen saturation but with the degree of depression. Several possible causal mechanisms linking OSA and depression have been proposed, although they have not been fully proven yet. They are as follows: 1) sleep fragmentation and hypoxia, two major phenomena of OSA that damage the brain, especially the hippocampus and frontal lobe (brain regions involved in maintaining daytime wakefulness, cognitive function, and mood, which thus trigger or worsen depression if damaged); 2) the level of serotonin is decreased in patients with depression, which also reduces genioglossus muscle activity via the hypoglossal nerve, compromising upper airway patency and causing OSA; and 3) inflammatory mediators such as interleukin 6 or tumor necrosis factor, which are increased in both OSA and depression, are suspected to increase daytime sleepiness.

In this study, we showed that the incidence of depression among patients with OSA was significantly increased.

<table>
<thead>
<tr>
<th>TABLE III.</th>
<th>Hazard Ratio of OSA on the Incidence of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Event</td>
</tr>
<tr>
<td>Control</td>
<td>804,200</td>
</tr>
<tr>
<td>OSA</td>
<td>160,840</td>
</tr>
<tr>
<td>No Surgery</td>
<td>141,067</td>
</tr>
<tr>
<td>UPPP</td>
<td>19,773</td>
</tr>
</tbody>
</table>

Model 1: adjusted by age and sex.  
Model 2: adjusted by age, sex, income level, diabetes, hypertension, and dyslipidemia.  
OSA = obstructive sleep apnea, UPPP = uvulopalatopharyngoplasty.

<table>
<thead>
<tr>
<th>TABLE IV.</th>
<th>Hazard Ratio of Covariates for Depression Incidence Among Patients With OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>OSA</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1 (Reference)</td>
</tr>
</tbody>
</table>

OSA = obstructive sleep apnea; UPPP = uvulopalatopharyngoplasty.
compared with controls. When patients with OSA underwent UPPP, the incidence of depression decreased to some extent but not to control levels. This finding may represent strong evidence that UPPP has a clinical effect independent of AHI-based judgment. A considerable strength of this study is that long-term follow-up was conducted across large-scale patient groups using national insurance data. Large-scale studies are essential to determine the deleterious effect of OSA on the incidence of depression and preventive effect of UPPP. Recently, Ishman et al. reported that the Beck depression index decreased after surgery in patients with OSA. However, the study was based on only 44 patients, and its mean follow-up period was very short: 115 days after surgery. Moreover, the surgery was not a single procedure but rather a multilevel one including nasal, oropharyngeal, and hypopharyngeal surgeries. Therefore, it was impossible to analyze the effect of UPPP alone. In contrast, we analyzed approximately 160 thousand OSA patients. Of those, about 20 thousand received UPPP in this study, and the follow-up period was more than 4 years.

There was a difference in the HR between the OSA and control groups and between the no surgery and UPPP groups according to sex; age; and accompanying diseases such as diabetes, hypertension, and dyslipidemia. Although it is not possible to analyze the exact reason, there are several explanations. Sex differences in OSA patients are well known, presumably because of differences in estrogen level, size and length of the upper airway, and fat distribution around it. The mortality rate of patients with OSA is age-dependent, with younger people having an increased mortality rate than older people after adjustment for age. This is probably because elderly patients, who have survived the long-standing hypoxia caused by OSA, become preconditioned for subsequent hypoxia better than young patients. Similarly, in the case of chronic diseases, such as diabetes, hypertension, and dyslipidemia, people with long-term illnesses may be more resistant to OSA than those without those illnesses.

The most significant weakness of this study is that the adequacy of the diagnosis and the severity of disease could not be demonstrated. We could not determine the adequacy of the diagnosis and the severity of disease on the basis of the diagnoses in the medical records. Fur- thermore, we did not know how many patients with OSA who did not undergo UPPP (the no surgery group) were offered alternative treatment such as CPAP or a mandibular advancing device (MAD). In Korea, UPPP is the preferred treatment of OSA rather than CPAP or MAD. Approximately 3 thousand patients are prescribed CPAP annually and its adherence rate is very low. Even fewer patients are prescribed MAD. Considering that the number of patients with OSA recruited in this study over 8 years was 160,840, it is reasonable to assume that most patients in the no surgery group did not receive active treatment for OSA and their condition naturally progressed. It is also a limitation of this study that the subtype of depression was not considered for the ease of analysis. Depression was simply defined when more than one claim was newly made with ICD-10 codes F32 or F33, which include all subtypes of depression except bipolar disorder.

CONCLUSION

OSA increases the incidence of depression. UPPP, a surgical treatment for OSA, appears to reduce the risk of comorbid depression.

BIBLIOGRAPHY