Association Between Cushing’s Syndrome and Sleep Apnea: Results From the National Inpatient Sample

Meghana Pattipati 1, Goutham Gudavalli 2

1. Internal Medicine, The Brooklyn Hospital Center, Brooklyn, USA 2. Critical Care Medicine, Rapides Regional Medical Center, Alexandria, USA

Corresponding author: Meghana Pattipati, megha.pattipati@gmail.com

Abstract

Background
Cushing’s syndrome is a metabolic disorder related to excess cortisol production. Patients with Cushing’s syndrome are at risk for the development of other comorbid medical conditions such as hypertension, diabetes, obesity, and obstructive sleep apnea. Obstructive sleep apnea has been well associated with endocrine disorders such as acromegaly and hypothyroidism. However, its causal association with Cushing’s syndrome is still unclear. We utilized a national database to study the prevalence of sleep apnea in Cushing’s syndrome.

Hypothesis
We hypothesized that patients with Cushing’s syndrome might have an increased prevalence of sleep apnea.

Methods
Patients aged above 18 years from the NIS database between 2017 and 2018 with a diagnosis of Cushing’s syndrome and sleep apnea were extracted using the 10th revision of the International Classification of Diseases (ICD-10) codes, with code E24 representing Cushing’s syndrome and G47.3 representing sleep apnea. The prevalence of sleep apnea and other comorbid medical conditions were identified using the ICD-10 codes. Logistic regression analysis was performed to examine the association between Cushing’s syndrome and sleep apnea.

Results
Cushing’s syndrome was prevalent in 0.037% (2,248 of 6,023,852) of all inpatient hospitalizations. Patients with Cushing’s syndrome were slightly younger (mean age: 54 ± 16 versus 58 ± 20) and more likely to be females (76%, 1,715 out of 2,248) and had higher rates of sleep apnea (21.9% versus 8.7%, p < 0.000) and obstructive sleep apnea (OSA) (18.6% versus 7.2%, p < 0.000) when compared to the general population. Cushing’s syndrome is independently associated with sleep apnea, with an unadjusted odds ratio (OR) of 2.94 (p < 0.01) and an adjusted odds ratio (aOR) of 1.79 after adjusting for demographics and other risk factors for sleep apnea and comorbid medical conditions (p < 0.01).

Conclusions
Cushing’s syndrome is associated with increased prevalence of sleep apnea and independent predictor of sleep apnea. Further prospective studies are recommended to validate the causal association. The high prevalence and coexistence of both these disorders validate screening for sleep apnea as part of routine workup in patients with Cushing’s syndrome and vice versa.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine, Neurology
Keywords: cushing’s syndrome, obesity, central sleep apnea, sleep apnea, osa

Introduction
Cushing’s syndrome is a metabolic disorder related to excess cortisol production. Patients with Cushing’s syndrome are at risk for the development of other comorbid medical conditions such as hypertension, diabetes, and obesity. Apnea is defined by the American Academy of Sleep Medicine (AASM) as the cessation of airflow for at least 10 seconds. Obstructive sleep apnea (OSA) and central sleep apnea are included under the umbrella, with OSA being the most common type of sleep apnea. Obstructive sleep apnea has been well associated with endocrine disorders such as acromegaly and hypothyroidism. However, its causal association with Cushing’s syndrome is still unclear. There are several different prospects regarding the development of sleep apnea in patients with Cushing’s syndrome, one of which could be secondary to impaired cortisol release. It has been studied in the literature that there is some association between sleep and cortisol release.
secretion. The exact mechanism of the prevalence or coexistence of sleep apnea, both central sleep apnea and obstructive sleep apnea, has not been well described. There are studies that found a relationship between Cushing’s syndrome and OSA. The correlation between obesity and fat tissue accumulation in the neck likely leads to the development of OSA in patients with Cushing’s syndrome/disease [1]. However, our study aimed to investigate if Cushing’s syndrome is an independent predictor of sleep apnea after adjusting for obesity and other comorbidities predisposing to sleep apnea. Parapharyngeal fat accumulation in Cushing’s syndrome/disease can cause sleep apnea, but no epidemiological information is available [2]. The very first association between OSA and Cushing’s syndrome was reported by Shipley et al. in 1992; 32% had mild sleep apnea (apnea-hypopnea index (AHI) > 9.4 events/hour), and 18% had >17.5 events/hour [3]. A nationwide longitudinal study done in Taiwan in 2017 investigated 1,612 patients with Cushing’s syndrome, and it showed a 2.82-fold increased risk of developing obstructive sleep apnea [4]. This study encourages further research into this association, as the mechanisms underlying this phenomenon remain unclear. Also, this study only included the incidence of OSA, but not sleep apnea in general, which included central sleep apnea and OSA [4]. A study conducted on women with Cushing’s syndrome found that women with Cushing’s syndrome are two times more likely to have obstructive sleep apnea, and cortisol was found to be an independent predictor of apnea-hypopnea index (AHI) after controlling for BMI and homeostasis model assessment (HOMA) score and plays a major role in the pathogenesis of OSA [5]. In a study conducted by Berger et al., three-month exogenous steroid therapy on an objective measure of sleep-disordered breathing showed that one out of 17 patients increased their mean AHI by 56%; however, the body weight, neck girth changes, and cumulative steroid doses were not correlated to the AHI increment [6]. Sleep apnea in Cushing’s syndrome could be secondary to impaired cortisol release. A study has shown the effect of the levels of serum cortisol on various stages of sleep, where REM sleep was found to be present when cortisol concentrations were decreasing, and wakefulness and stage 1 sleep are associated with increased cortisol concentrations [6].

Our research aims to address the question of whether sleep apnea should be considered independent comorbidity of Cushing’s syndrome and should screening for OSA be part of the routine workup for patients with Cushing’s syndrome. OSA comorbidity in Cushing’s syndrome can be a risk factor for increased morbidity and mortality and might have a major effect on the quality of life.

Materials And Methods

Data source
We utilized the AHRQ’s NIS database, which is developed as part of the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest all-payer inpatient healthcare database in the United States. It included data from approximately seven million patient hospital stays per year from over 1,000 hospitals and is a representative sample of about 20% of nonfederal hospitals in the United States.

Patient population
Data capture in the NIS databases from 2017 to 2018 was utilized for this analysis. All patients above 18 years of age with a diagnosis of Cushing’s syndrome were identified using the Clinical Classification Software (CCS) codes. The CCS is a categorization scheme that groups the 10th revision of the International Classification of Diseases (ICD-10) codes into mutually exclusive categories. CCS code E24 represents all ICD-10 diagnoses of Cushing’s syndrome. The sleep apnea group included all kinds of sleep apnea, including central and obstructive sleep apnea, and other causes representing the ICD-10 diagnostic code of G47.3, whereas obstructive sleep apnea is separately represented by code OSA G47.33. All the above diagnostic codes were obtained if it was included in the 40 diagnostic codes listed in the database.

The baseline demographics and social variables examined in the study included age, gender, race, smoking, alcohol, various comorbidities (hypertension, diabetes, obesity, liver disease, chronic lung disease, chronic kidney disease/end-stage renal disease, cerebral infarction, heart failure, cardiac arrhythmias, thyroid disorder, obesity hypoventilation syndrome (OHS), restless leg syndrome (RLS), and fluid, electrolyte, and acid-base disorders), social factors such as insurance payer, hospital bed size, socioeconomic status based on household income, location and region of the hospital, and teaching status of the hospital.

Statistical analysis
The primary outcome of the study is to estimate the prevalence of sleep apnea and OSA in patients diagnosed with Cushing’s syndrome and predict the independent association after adjusting for other parameters such as obesity, substance use (smoking and alcohol), and underlying comorbidities. All analyses were performed using STRATA/SE 17.0. Univariate analysis was performed initially to estimate the individual risk factors and predictors for Cushing’s syndrome using logistic regression for numerical covariates and weighted chi-square tests for categorical covariates. Multivariate logistic regression analysis was performed based on the univariate analysis to predict the adjusted odds ratio (aOR) for each variable of interest.

Results
Cushing’s syndrome was prevalent in 2,248 of 6,023,852 hospitalized patient samples, estimating the prevalence to be 0.037%. Sleep apnea was diagnosed in 493 patients among the 2,248 (21.9%) compared with 525,079 among the 6,021,604 (8.7%) of the general population (control). Table 1 lists the baseline demographics of patients in both groups of patients with and without Cushing’s syndrome. Significant differences were found between both groups, with patients in the Cushing’s syndrome group being slightly younger compared to the general population (mean age ± SD: 54 ± 16 versus 58 ± 20, p < 0.01). The majority of them were females (76% versus 57%), and Cushing’s syndrome is more prevalent in the White population (73% versus 67%). The prevalence of certain comorbidities was higher in the Cushing’s syndrome group versus the general population (diabetes: 47.5% versus 27.5%, obesity: 41% versus 16.8%, hypertension: 69.7% versus 56.6%, chronic lung disease: 35.6% versus 22.6%, chronic kidney disease/end-stage renal disease: 19.4% versus 17.2%, chronic liver disease: 7.7% versus 5.5%, heart failure: 24% versus 17.7%, sleep apnea: 21.9% versus 8.7%, OSA: 18.6% versus 7.2%, OHS: 3.6% versus 0.6%, thyroid disorders: 24.6% versus 13.4%).

Patients in the Cushing’s syndrome group have fallen into the higher socioeconomic status category in terms of higher income compared with the control (less than 50th percentile group: 57% versus 52%, with major difference noted in the private insurance group, 33.4% in the Cushing’s syndrome group versus 26.3% among others).

|                | Control (general population) (N = 6,021,604) | Control (general population) (% = 99.96%) | Cushing’s syndrome (N = 2,248) | Cushing’s syndrome (% = 0.037%) | P value |
|----------------|---------------------------------------------|------------------------------------------|--------------------------------|---------------------------------|---------|
| Sex: Male      | Reference                                   |                                          |                                |                                 |         |
| Female         | 3,450,511                                   | 57%                                      | 1,715                          | 76%                             | <0.001  |
| Age in years   |                                             |                                          |                                |                                 |         |
| 18–19          | 43,436                                      | 0.7%                                     | 18                             | 0.8%                            | <0.001  |
| ≥20 and <30    | 651,487                                     | 10.8%                                    | 167                            | 7.4%                            | <0.001  |
| ≥30 and <40    | 715,922                                     | 11.9%                                    | 287                            | 12.7%                           | <0.001  |
| ≥40 and <50    | 541,640                                     | 9%                                       | 358                            | 15.9%                           | <0.001  |
| ≥50 and <60    | 870,878                                     | 14.5%                                    | 513                            | 22.8%                           | 0.144   |
| ≥60 and <70    | 1,128,762                                   | 18.7%                                    | 507                            | 22.5%                           | <0.001  |
| ≥70 and <80    | 1,073,623                                   | 17.8%                                    | 294                            | 13%                             | <0.001  |
| ≥80 and <90    | 747,084                                     | 12.4%                                    | 96                             | 4.3%                            | <0.001  |
| ≥90 and <100   | 248,500                                     | 4.1%                                     | 8                              | 0.35%                           | <0.001  |
| Mean age in years at admission (mean ± SD) | 58 ± 20                                    | 54 ± 16                                  |                                |                                 |         |
| Diabetes       | 1,653,951                                   | 27.5%                                    | 1,069                          | 47.5%                           | <0.001  |
| Obesity        | 1,013,497                                   | 16.8%                                    | 923                            | 41%                             | <0.001  |
| Hypertension   | 3,410,907                                   | 56.6%                                    | 1,567                          | 69.7%                           | <0.001  |
| Chronic lung disease | 1,361,787     | 22.6%                                    | 801                            | 35.6%                           | <0.001  |
| Chronic kidney disease/ESRD | 1,035,714       | 17.2%                                    | 436                            | 19.4%                           | <0.008  |
| Liver disease  | 329,552                                     | 5.5%                                     | 173                            | 7.7%                            | <0.09   |
| Cerebral infarction | 134,560         | 2.2%                                     | 47                             | 2.1%                            | <0.304  |
| Heart failure  | 1,066,315                                   | 17.7%                                    | 540                            | 24%                             | <0.001  |
| Sleep apnea    | 525,079                                     | 8.7%                                     | 493                            | 21.9%                           | <0.001  |
| Obstructive sleep apnea | 433,303     | 7.2%                                     | 418                            | 18.6%                           | <0.542  |
| Obesity hypoventilation syndrome | 36,554       | 0.6%                                     | 81                             | 3.6%                            | <0.001  |
| Category                                | Count   | Percentage | Median | P-Value |
|-----------------------------------------|---------|------------|--------|---------|
| Thyroid disorders                       | 809,272 | 13.4%      | 554    | <0.001  |
| Fluid, electrolyte, and acid-base       | 1,510,937 | 25%       | 831    | <0.001  |
| abnormalities                           |         |            |        |         |
| Atrial fibrillation/flutter              | 948,272 | 15.7%      | 293    | <0.026  |
| Other cardiac arrhythmias               | 110,723 | 1.8%       | 36     | <0.423  |
| RLS                                     | 74,719  | 1.24%      | 48     | <0.001  |
| Smoking                                 | 1,009,738 | 16.7%    | 270    | <0.001  |
| Household income (percentile)           |         |            |        |         |
| 0–25th                                  | 1,753,964 | 30%       | 541    | <0.001  |
| 26th–50th                               | 1,599,032 | 27%       | 615    | <0.001  |
| 51st–75th                               | 1,406,404 | 23.7%     | 582    | <0.001  |
| 76th–100th                              | 1,154,711 | 19.5%     | 480    | <0.001  |
| Race                                    |         |            |        |         |
| White                                   | 3,933,806 | 67%       | 1,808  | <0.001  |
| Black                                   | 884,709  | 15%        | 244    | <0.001  |
| Hispanic                                | 673,605  | 11.5%      | 212    | <0.001  |
| Asian/Pacific Island                    | 163,754  | 2.8%       | 60     | <0.271  |
| Native American                         | 38,039   | 0.6%       | 14     | <0.293  |
| Other                                   | 177,439  | 3%         | 60     | <0.144  |
| Pay                                     |         |            |        |         |
| Medicare                                | 2,902,371 | 48.3%     | 1,035  | <0.001  |
| Medicaid                                | 1,089,273 | 18%       | 340    | <0.001  |
| Private                                 | 1,586,714 | 26.3%     | 751    | <0.039  |
| Self-pay                                | 247,165   | 4.1%       | 71     | <0.001  |
| No charge                               | 21,637   | 0.35%      | 1      | <0.038  |
| Other                                   | 166,460   | 2.76%      | 47     | <0.015  |
| Location of hospital/teaching status    |         |            |        |         |
| Rural                                   | 537,907   | 8.9%       | 180    | <0.001  |
| Urban non-teaching                      | 1,252,816 | 20.8%     | 375    | <0.747  |
| Urban teaching                          | 4,230,881 | 70%       | 1,713  | <0.001  |
| Bed size                                |         |            |        |         |
| Small                                   | 1,277,522 | 21%       | 387    | <0.001  |
| Medium                                  | 1,758,086 | 29%       | 601    | <0.107  |
| Large                                   | 2,985,996 | 49.6%      | 1,260  | <0.001  |
| Hospital region                         |         |            |        |         |
| Northeast                               | 118,422   | 2%        | 461    | <0.001  |
| Midwest                                 | 1,345,585 | 22%       | 537    | <0.004  |
| South                                   | 2,382,075 | 39.5%     | 815    | <0.002  |
| West                                    | 1,175,522 | 19.5%     | 435    | <0.062  |
Table 1: Baseline demographics of the general population with and without Cushing’s syndrome

|                              | General population without sleep apnea (N = 5,498,280) | General population without sleep apnea (% = 91.28%) | Sleep apnea (N = 525,572) | Sleep apnea (% = 8.72%) | P value |
|------------------------------|--------------------------------------------------------|---------------------------------------------------|---------------------------|-------------------------|---------|
| **Sex**                      |                                                        |                                                   |                           |                         |         |
| Male                         | 2,273,084                                              | 41.3%                                             | 297,995                   | 56.7%                   | <0.001  |
| Female                       | 3,224,674                                              | 58.6%                                             | 227,552                   | 43.3%                   | <0.001  |
| **Age in years**             |                                                        |                                                   |                           |                         |         |
| 18–19                        | 43,070                                                 | 0.78%                                             | 384                       | 0.07%                   | <0.001  |
| ≥20 and <30                  | 645,291                                                | 11.7%                                             | 6,363                     | 1.2%                    | 0.489   |
| ≥30 and <40                  | 696,535                                                | 12.7%                                             | 19,674                    | 3.7%                    | <0.001  |
| ≥40 and <50                  | 493,839                                                | 9%                                                | 48,159                    | 9.2%                    | <0.001  |
| ≥50 and <60                  | 767,841                                                | 14%                                               | 103,550                   | 19.7%                   | <0.001  |
| ≥60 and <70                  | 978,539                                                | 17.8%                                             | 150,730                   | 28.7%                   | <0.001  |
| ≥70 and <80                  | 940,113                                                | 17%                                               | 133,804                   | 25.4%                   | <0.001  |
| ≥80 and <90                  | 691,539                                                | 12.6%                                             | 55,641                    | 10.6%                   | 0.606   |
| ≥90 and <100                 | 241,249                                                | 4.4%                                              | 7,259                     | 1.4%                    | <0.001  |
| Mean age in years at admission (mean ± SD) | 57±20                                                  |                                                   | 64±13                     |                         |         |
| Cushing’s syndrome           | 1,755                                                  | 0.03%                                             | 493                       | 0.08%                   | <0.001  |
| Diabetes                     | 1,402,449                                              | 25.5%                                             | 252,571                   | 48%                     | <0.001  |
| Obesity                      | 760,175                                                | 13.8%                                             | 254,245                   | 48.4%                   | <0.001  |
| Hypertension                 | 2,983,757                                              | 54.3%                                             | 428,717                   | 81.6%                   | <0.001  |
| Chronic lung disease         | 1,151,029                                              | 21%                                               | 211,559                   | 40%                     | <0.001  |
| Chronic kidney disease/ESRD  | 891,063                                                | 16.2%                                             | 145,087                   | 27.6%                   | <0.001  |
| Liver disease                | 295,925                                                | 5.4%                                              | 33,800                    | 6.4%                    | <0.001  |
| Cerebral infarction          | 124,201                                                | 2.25%                                             | 10,406                    | 2%                      | <0.001  |

Table 2 describes the baseline patient characteristics in the patient population with and without sleep apnea. Sleep apnea was more prevalent in Whites (75.7% versus 66%) and in patients who are slightly older than the general population (mean age ± SD: 64 ± 13 versus 57 ± 20). Unlike Cushing’s syndrome, sleep apnea is more prevalent in males than in females, with female cases accounting for 43% versus 58.6% in the general population. The comorbidities that are more prevalent in the sleep apnea group compared with the control group were diabetes (48% versus 25.5%), obesity (48.4% versus 13.8%), hypertension (81.6% versus 54.3%), Cushing’s syndrome (0.09% versus 0.03%), chronic lung disease (40% versus 21%), chronic kidney disease/ESRD (27.6% versus 16.2%), chronic liver disease (6.4% versus 5.4%), heart failure (54% versus 16%), atrial fibrillation (27.8% versus 14.6%), other cardiac arrhythmias (2.8% versus 1.74%), obesity hypoventilation syndrome (1.35% versus 0.5%), thyroid disorders (18.6% versus 13%), and restless leg syndrome (3.7% versus 1%).

The comorbidities that are less prevalent in sleep apnea patients compared with the control group were cerebral infarction (2% versus 2.25%), smoking (13.5% versus 17%), and alcohol-related disorders (3.4% versus 6.3%). Patients in the sleep apnea group were relatively under the low socioeconomic group with Medicare, Medicaid, and self-pay being the primary insurance type (78.4% versus 70.3%).
| Condition                                      | Count   | Percent | Median follow-up months | p-value |
|-----------------------------------------------|---------|---------|-------------------------|---------|
| Heart failure                                 | 887,719 | 16%     | 179,136                 | <0.001  |
| Obesity hypoventilation syndrome              | 29,510  | 0.5%    | 7,125                   | <0.001  |
| Thyroid disorders                             | 711,727 | 13%     | 98,099                  | <0.001  |
| Fluid, electrolyte, and acid-base disorders    | 1,373,143| 25%     | 138,625                 | <0.001  |
| Atrial fibrillation/flutter                    | 802,520 | 14.6%   | 146,045                 | <0.001  |
| Other cardiac arrhythmias                     | 95,881  | 1.74%   | 14,878                  | <0.001  |
| RLS                                           | 55,020  | 1%      | 19,747                  | <0.001  |
| Smoking                                       | 939,200 | 17%     | 70,808                  | <0.001  |
| Alcohol-related disorders                     | 346,704 | 6.3%    | 17,930                  | <0.001  |
| Household income (percentile)                 |         |         |                         |         |
| 0–25th                                        | 1,612,954| 29.9%   | 141,551                 | <0.001  |
| 26th–50th                                     | 1,455,384| 27%     | 144,263                 | <0.001  |
| 51st–75th                                     | 1,275,260| 23.6%   | 131,726                 | <0.001  |
| 76th–100th                                    | 1,054,593| 19.5%   | 100,598                 | <0.001  |
| Race                                          |         |         |                         |         |
| White                                         | 3,547,515| 66%     | 387,899                 | <0.001  |
| Black                                         | 812,434 | 15%     | 72,519                  | <0.001  |
| Hispanic                                      | 639,660 | 12%     | 34,157                  | <0.001  |
| Asian/Pacific Island                          | 157,786 | 3%      | 6,028                   | <0.001  |
| Native American                               | 35,345  | 0.65%   | 2,708                   | <0.001  |
| Other                                         | 168,548 | 3.14%   | 8,951                   | <0.001  |
| Pay                                           |         |         |                         |         |
| Medicare                                      | 2,581,830| 47%     | 321,576                 | <0.001  |
| Medicaid                                      | 1,039,816| 19%     | 49,797                  | <0.001  |
| Private                                       | 1,457,309| 26.5%   | 130,156                 | 0.763   |
| Self-pay                                      | 238,318 | 4.3%    | 8,918                   | <0.001  |
| No charge                                     | 20,971  | 0.4%    | 667                     | <0.001  |
| Other                                         | 152,653 | 2.8%    | 13,854                  | <0.001  |
| Location of hospital/teaching status          |         |         |                         |         |
| Rural                                         | 495,305 | 9%      | 42,762                  | <0.001  |
| Urban non-teaching                            | 1,148,887| 20.9%   | 104,304                 | <0.001  |
| Urban teaching                                | 3,854,088| 70.1%   | 378,506                 | <0.001  |
| Bed size                                      |         |         |                         |         |
| Small                                         | 1,167,980| 21.2%   | 109,929                 | <0.001  |
| Medium                                        | 1,608,347| 29.2%   | 150,340                 | <0.001  |
| Large                                         | 2,721,953| 49.5%   | 265,303                 | <0.001  |
| Hospital region                               |         |         |                         |         |
| Region       | Count   | Overall % | Unadjusted odds ratio (CI) | Adjusted odds ratio (CI) | P value |
|--------------|---------|-----------|----------------------------|--------------------------|---------|
| Northeast    | 1,033,267 | 18.8% | 0.53 (0.53–0.54) | 0.55 (0.54–0.55) | <0.001 |
| Midwest      | 1,192,925 | 21.7% | 3.16 (2.86–3.50) | 4.54 (4.09–5.04) | <0.001 |
| South        | 2,189,730 | 40%   | 10.9 (9.88–12.09) | 15.12 (13.7–16.72) | <0.001 |
| West         | 1,082,358 | 19.7% | 0.50 (0.49–0.51) | 0.55 (0.54–0.55) | <0.001 |

**Independent variables associated with sleep apnea**

| Variable                      | Unadjusted odds ratio (CI) | P value | Adjusted odds ratio (CI) | P value |
|-------------------------------|-----------------------------|---------|--------------------------|---------|
| Sex                           |                             |         |                          |         |
| Male                          |                             |         |                          |         |
| Female                        | 0.53 (0.53–0.54)            | <0.001  | 0.55 (0.54–0.55)         | <0.001  |
| Age in years                  |                             |         |                          |         |
| 18–19                         |                             |         |                          |         |
| ≥20 and <30                   | 1.10 (0.99–1.22)            | 0.056   | 1.03 (0.93–1.15)         | 0.589   |
| ≥30 and <40                   | 3.16 (2.86–3.50)            | <0.001  | 2.23 (2.01–2.48)         | <0.001  |
| ≥40 and <50                   | 10.9 (9.88–12.09)           | <0.001  | 4.54 (4.09–5.04)         | <0.001  |
| ≥50 and <60                   | 15.12 (13.7–16.72)          | <0.001  | 4.82 (4.34–5.34)         | <0.001  |
| ≥60 and <70                   | 17.27 (15.7–19.10)          | <0.001  | 4.32 (3.89–4.79)         | <0.001  |
| ≥70 and <80                   | 15.96 (14.27–17.7)          | <0.001  | 3.52 (3.17–3.91)         | <0.001  |
| ≥80 and <90                   | 9.02 (8.15–9.98)            | <0.001  | 2.15 (1.94–2.39)         | <0.001  |
| ≥90 and <100                  | 3.37 (3.04–3.74)            | <0.001  | 0.97 (0.87–1.08)         | 0.606   |
| Cushing’s syndrome            |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 2.94 (2.66–3.24)            | <0.001  | 1.79 (1.60–2.01)         | <0.001  |
| Diabetes                      |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 2.70 (2.68–2.71)            | <0.001  | 1.38 (1.37–1.39)         | <0.001  |
| Obesity                       |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 5.84 (5.80–5.97)            | <0.001  | 4.59 (4.56–4.62)         | <0.001  |
| Hypertension                  |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 3.73 (3.70–3.75)            | <0.001  | 1.70 (1.68–1.71)         | <0.001  |
| Chronic lung disease          |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 2.54 (2.52–2.55)            | <0.001  | 1.96 (1.94–1.97)         | <0.001  |
| Chronic kidney disease/ESRD   |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 1.97 (1.95–1.98)            | <0.001  | 1.05 (1.04–1.06)         | <0.001  |
| Liver disease                 |                             |         |                          |         |
| No                            |                             |         |                          |         |
| Yes                           | 1.20 (1.19–1.22)            | <0.001  | 1.05 (1.04–1.07)         | <0.001  |
| Cerebral infarction           |                             |         |                          |         |

2022 Pattipati et al. Cureus 14(2): e22044. DOI 10.7759/cureus.22044
| Condition                          | Reference | Yes                  | P-value | Yes                  | P-value |
|-----------------------------------|-----------|----------------------|---------|----------------------|---------|
| **Heart failure**                 | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 0.87 (0.85–0.89)     | <0.001  | 0.77 (0.75–0.78)     | <0.001  |
| Obesity hypoventilation syndrome  | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 2.68 (2.66–2.70)     | <0.001  | 1.43 (1.42–1.44)     | <0.001  |
| Thyroid disorders                 | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 2.54 (2.48–2.61)     | <0.001  | 0.39 (0.38–0.40)     | <0.001  |
| Fluid, electrolyte, and acid–base disorders | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 1.54 (1.53–1.55)     | <0.001  | 1.28 (1.27–1.29)     | <0.001  |
| Atrial fibrillation/flutter       | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 2.25 (2.23–2.26)     | <0.001  | 1.42 (1.41–1.43)     | <0.001  |
| Other cardiac arrhythmias         | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 1.64 (1.61–1.67)     | <0.001  | 1.14 (1.12–1.16)     | <0.001  |
| RLS                               | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 3.86 (3.79–3.92)     | <0.001  | 2.68 (2.63–2.73)     | <0.001  |
| Smoking                           | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 0.75 (0.74–0.76)     | <0.001  | 0.69 (0.69–0.70)     | <0.001  |
| Alcohol use                       | Reference |                      |         |                      |         |
| No                                |           |                      |         |                      |         |
| Yes                               |           | 0.52 (0.51–0.53)     | <0.001  | 0.61 (0.60–0.62)     | <0.001  |
| Household income (percentile)     | Reference |                      |         |                      |         |
| 0–25th                            |           |                      |         |                      |         |
| 26th–50th                         |           | 1.12 (1.12–1.13)     | <0.001  | 1.10 (1.09–1.11)     | <0.001  |
| 51st–75th                         |           | 1.17 (1.16–1.18)     | <0.001  | 1.18 (1.17–1.19)     | <0.001  |
| 76th–100th                        |           | 1.08 (1.07–1.09)     | <0.001  | 1.24 (1.22–1.25)     | <0.001  |
| Race                              | Reference |                      |         |                      |         |
| White                             |           |                      |         |                      |         |
| Black                             |           | 0.81 (0.80–0.82)     | <0.001  | 0.86 (0.85–0.87)     | <0.001  |
| Hispanic                          |           | 0.48 (0.482–0.493)   | <0.001  | 0.64 (0.63–0.64)     | <0.001  |
| Asian/Pacific Island              |           | 0.34 (0.340–0.358)   | <0.001  | 0.50 (0.49–0.51)     | <0.001  |
| Native American                   |           | 0.70 (0.67–0.72)     | <0.001  | 0.80 (0.76–0.83)     | <0.001  |
| Independent variables associated with sleep apnea | Unadjusted odds ratio (CI) | P value | Adjusted odds ratio (CI) | P value |
|-------------------------------------------------|---------------------------|---------|--------------------------|---------|
| Sex                                             |                           |         |                          |         |
| Male                                            |                           | <0.001  |                          | <0.001  |
| Female                                          |                           | >0.05   |                          | >0.05   |
| Age in years                                     |                           |         |                          |         |
| 18–19                                           |                           | <0.001  |                          | <0.001  |

Table 3 describes the odds ratio (OR) and the adjusted odds ratio (aOR) of sleep apnea and the variables of interest. The odds of exposure to certain risk factors were calculated for sleep apnea, and the results showed that sleep apnea is independently associated with the following conditions. Cushing’s syndrome is found to have an independent association with sleep apnea, with an unadjusted odds ratio of 2.94 and an adjusted odds ratio of 1.79 after adjusting for multiple risk factors. Obesity had the strongest association with sleep apnea (OR = 5.84, 95%CI = 5.80–5.97; aOR = 4.59, 95%CI = 4.56–4.62), followed by chronic lung disease (OR = 5.54, 95%CI = 5.22–5.85; aOR = 3.96, 95%CI = 3.94–3.98), hypertension (OR = 3.73, 95%CI = 3.70–3.75; aOR = 1.70, 95%CI = 1.68–1.71), restless leg syndrome (OR = 3.86, 95%CI = 3.79–3.92; aOR = 1.70, 95%CI = 1.69–1.71), diabetes (OR = 2.70, 95%CI = 2.68–2.71; aOR = 1.8, 95%CI = 1.77–1.83), heart failure (OR = 2.8, 95%CI = 2.76–2.84; aOR = 1.8, 95%CI = 1.77–1.83), atrial fibrillation/atrial flutter (OR = 2.25, 95%CI = 2.23–2.26; aOR = 1.8, 95%CI = 1.79–1.81), other cardiac arrhythmias (OR = 1.64, 95%CI = 1.61–1.67; aOR = 1.8, 95%CI = 1.79–1.81), thyroid disorders (OR = 1.54, 95%CI = 1.53–1.55; aOR = 1.28, 95%CI = 1.27–1.29), chronic kidney disease/ESRD (OR = 1.97, 95%CI = 1.95–1.98; aOR = 1.97, 95%CI = 1.95–1.98), and chronic liver disease (OR = 2.0, 95%CI = 1.98–2.02; aOR = 1.97, 95%CI = 1.95–1.98). Univariate and multivariate analyses were performed for the statistical significance of these conditions.
| Age Group          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| ≥20 and <30       | 1.10   | (0.99–1.22)  | 0.056   |
| 30 and <40        | 3.16   | (2.86–3.50)  | <0.001  |
| 40 and <50        | 10.9   | (9.88–12.09) | <0.001  |
| 50 and <60        | 15.12  | (13.7–16.72) | <0.001  |
| 60 and <70        | 17.27  | (15.7–19.10) | <0.001  |
| 70 and <80        | 15.96  | (14.43–17.7) | <0.001  |
| 80 and <90        | 9.02   | (8.15–9.98)  | <0.001  |
| 90 and <100       | 3.37   | (3.04–3.74)  | <0.001  |

Cushing’s syndrome

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 2.94   | (2.66–3.24)  | <0.001  |

Diabetes

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 2.70   | (2.68–2.71)  | <0.001  |

Obesity

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 5.84   | (5.80–5.97)  | <0.001  |

Hypertension

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 3.73   | (3.70–3.75)  | <0.001  |

Chronic lung disease

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 2.54   | (2.52–2.55)  | <0.001  |

Chronic kidney disease/ESRD

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 1.97   | (1.95–1.98)  | <0.001  |

Liver disease

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 1.20   | (1.19–1.22)  | <0.001  |

Cerebral infarction

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 0.87   | (0.85–0.89)  | <0.001  |

Heart failure

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 2.68   | (2.66–2.70)  | <0.001  |

Obesity hypoventilation syndrome

| Presence          | RR     | 95% CI        | p Value |
|-------------------|--------|--------------|---------|
| No                | Reference |
| Yes               | 2.54   | (2.48–2.61)  | <0.001  |

Thyroid disorders
| Condition                                | Yes (Reference) | p-value | Yes (Reference) | p-value |
|------------------------------------------|-----------------|---------|-----------------|---------|
| Fluid, electrolyte, and acid–base disorders | 1.54 (1.53–1.55) | <0.001  | 1.28 (1.27–1.29) | <0.001  |
| Atrial fibrillation/flutter              | 1.07 (1.06–1.08) | <0.001  | 0.80 (0.79–0.80) | <0.001  |
| Other cardiac arrhythmias                | 2.25 (2.23–2.28) | <0.001  | 1.42 (1.41–1.43) | <0.001  |
| RLS                                      | 1.64 (1.61–1.67) | <0.001  | 1.14 (1.12–1.16) | <0.001  |
| Smoking                                  | 0.75 (0.74–0.76) | <0.001  | 0.69 (0.69–0.70) | <0.001  |
| Alcohol use                              | 0.52 (0.51–0.53) | <0.001  | 0.61 (0.60–0.62) | <0.001  |
| Household income (percentile)            |                 |         |                 |         |
| 0–25th                                   |                 |         |                 |         |
| 26th–50th                                | 1.12 (1.12–1.13) | <0.001  | 1.10 (1.09–1.11) | <0.001  |
| 51st–75th                                | 1.17 (1.16–1.18) | <0.001  | 1.18 (1.17–1.19) | <0.001  |
| 76th–100th                               | 1.08 (1.07–1.09) | <0.001  | 1.24 (1.22–1.25) | <0.001  |
| Race                                     |                 |         |                 |         |
| White                                    |                 |         |                 |         |
| Black                                    | 0.81 (0.80–0.82) | <0.001  | 0.86 (0.85–0.87) | <0.001  |
| Hispanic                                 | 0.48 (0.482–0.493) | <0.001  | 0.64 (0.63–0.64) | <0.001  |
| Asian/Pacific Island                     | 0.34 (0.340–0.358) | <0.001  | 0.50 (0.49–0.51) | <0.001  |
| Native American                          | 0.70 (0.67–0.72) | <0.001  | 0.80 (0.76–0.83) | <0.001  |
| Other                                    | 0.48 (0.47–0.49) | <0.001  | 0.64 (0.62–0.65) | <0.001  |
| Pay                                      |                 |         |                 |         |
| Medicare                                 |                 |         |                 |         |
| Medicaid                                 | 0.384 (0.38–0.388) | <0.001  | 0.69 (0.68–0.70) | <0.001  |
| Private                                  | 0.71 (0.71–0.72) | <0.001  | 0.99 (0.98–1.00) | 0.763   |
| Self-pay                                 | 0.30 (0.29–0.30) | <0.001  | 0.52 (0.51–0.53) | <0.001  |
| No charge                                | 0.25 (0.23–0.27) | <0.001  | 0.43 (0.39–0.47) | <0.001  |
| Other                                    | 0.72 (0.71–0.74) | <0.001  | 0.96 (0.94–0.98) | <0.001  |

Location of hospital/teaching status

2022 Pattipati et al. Cureus 14(2): e22044. DOI 10.7759/cureus.22044
TABLE 3: Adjusted odds ratio for each independent variable associated with sleep apnea

| Rural                  | Reference | 1.05 (1.03–1.06) | <0.001 | 1.05 (1.03–1.06) | <0.001 |
|------------------------|-----------|------------------|--------|------------------|--------|
| Urban non-teaching     | Reference | 1.13 (1.12–1.14) | <0.001 | 1.20 (1.18–1.21) | <0.001 |
| Urban teaching         |           | 1.05 (1.03–1.06) | <0.001 | 1.05 (1.03–1.06) | <0.001 |

| Bed size               | Reference | 0.99 (0.98–1.00) | <0.001 | 1.03 (1.02–1.04) | <0.001 |
|------------------------|-----------|------------------|--------|------------------|--------|
| Medium                 |           | 1.03 (1.02–1.04) | <0.001 | 1.06 (1.06–1.07) | <0.001 |
| Large                  |           | 1.03 (1.02–1.04) | <0.001 | 1.06 (1.06–1.07) | <0.001 |

| Hospital region        | Reference | 1.54 (1.53–1.56) | <0.001 | 1.40 (1.39–1.42) | <0.001 |
|------------------------|-----------|------------------|--------|------------------|--------|
| Midwest                |           | 1.06 (1.05–1.07) | <0.001 | 1.10 (1.09–1.11) | <0.001 |
| South                  |           | 1.04 (1.05–1.06) | <0.001 | 1.23 (1.22–1.24) | <0.001 |
| West                   |           | 1.04 (1.05–1.06) | <0.001 | 1.23 (1.22–1.24) | <0.001 |

**Discussion**

Cushing’s syndrome is an independent risk factor for the development of sleep apnea. Oftentimes, both conditions are coexistent, and the burden of unrecognized and untreated sleep apnea on health-related quality of life is well known. Sleep apnea still remains an underdiagnosed medical condition, and this study reinforces the basic necessity to screen for sleep apnea during routine clinical practice in high-risk patients, including those with Cushing’s syndrome. The morbidity and mortality of untreated sleep apnea are well known and could have a slightly higher effect in subpopulation groups such as those with Cushing’s syndrome.

In a meta-analysis of 637 participants with OSA, CPAP treatment significantly reduced both plasma and salivary cortisol levels. Individuals undergoing investigation for Cushing’s syndrome would benefit from an initial screening for OSA; the impact of CPAP on cortisol has been debatable because of conflicting findings between studies due to small sample sizes [7]. The mechanism of correlation between sleep apnea and Cushing’s disease/Cushing’s syndrome have never been investigated; it has been suggested that weight gain and adipose tissue accumulation according to a centripetal pattern in the subcutaneous tissue of the neck can likely lead to the development of obstructive sleep apnea in these patient population. The neck and waist circumference are highly predictive of OSA severity [8,9].

Our study is the largest to date to evaluate patients with Cushing’s syndrome and sleep apnea in the United States. The underlying pathophysiology of the link between these two disease processes is yet to be determined, and further prospective studies have to be conducted to study the exact pathophysiology of the association. This is a large sample study with statistically significant results. Despite the large power afforded by the large number of patients available in NIS, there are several significant limitations of this study; given that this database is based on administrative coding, not all clinical data are available for analysis. For this reason, it is not possible to definitely identify if patients with sleep apnea developed Cushing’s syndrome or patients with Cushing’s syndrome developed sleep apnea later. Also, the treatment options and apnea-hypopnea index (AHI) determining the severity of sleep apnea were also not included. Most of the patients with sleep apnea or Cushing’s syndrome without any underlying comorbidities might not have been hospitalized, which underpredicts the overall prevalence. Our findings however highlight the need for further prospective studies to clarify the coexistence of these two disorders and the need for incorporating routine screening for either condition in patients diagnosed with one of those to improve the outcomes in these patient populations. Another limitation of our analysis is that the NIS does not capture individual treatment data, and thus, we are unable to explore the utility of treating sleep apnea (e.g., CPAP in the case of OSA) or treating the underlying medical conditions (e.g., heart failure in central sleep apnea), and the treatment of Cushing’s syndrome could have any influence on the prevalence of these diseases.

**Conclusions**

The morbidity and mortality of untreated sleep apnea are well known and could have a slightly higher negative impact on the outcomes in subpopulation groups such as those with Cushing’s syndrome. Oftentimes, as clinicians, we have tunnel vision and overlook underlying coexisting medical conditions, especially disorders such as obstructive sleep apnea. OSA is one of the medical disorders that is often missed...
during diagnosis and is the most common underrecognized and underdiagnosed medical condition. This study sheds light on sleep apnea and the importance of screening it among patients diagnosed with Cushing’s syndrome. This study also helps bring awareness regarding the possibility of an association between Cushing’s syndrome and sleep apnea among physicians in different fields of practice, including internal medicine, family medicine, sleep medicine, endocrine, and neurology, while caring for patients in their respective areas of practice.

**Additional Information**

**Disclosures**

**Human subjects:** All authors have confirmed that this study did not involve human participants or tissue.

**Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue.

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following:

**Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work.

**Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

**Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**Acknowledgements**

Both authors have contributed equally to the work and should be considered co-first authors.

**References**

1. Bottini P, Tantucci C: Sleep apnea syndrome in endocrine diseases. Respiration. 2003, 70:520-7. [10.1159/000072019]

2. Rosenn F, McCarthy V, Caruso AC: Sleep apnoea in endocrine diseases. J Sleep Res. 1998, 7:3-11. [10.1046/j.1355-2869.1998.00086.x]

3. Shipley JE, Schteingart DE, Tandon R, Starkman MN: Sleep architecture and sleep apnea in patients with Cushing's disease. Sleep. 1992, 15:514-8. [10.1093/sleep/15.6.514]

4. Wang LU, Wang TY, Bai YM, et al.: Risk of obstructive sleep apnea among patients with Cushing's syndrome: a nationwide longitudinal study. Sleep Med. 2017, 36:44-7. [10.1016/j.sleep.2017.04.016]

5. Risk for sleep apnea doubles in women with Cushing's syndrome. (2016). Accessed: December 20, 2021: [https://www.healio.com/news/endocrinology/20161220/risk-for-sleep-apnea-doubles-in-women-with-cushings-syndrome](https://www.healio.com/news/endocrinology/20161220/risk-for-sleep-apnea-doubles-in-women-with-cushings-syndrome).

6. Berger G, Hardak E, Shaham B, Avitan E, Yigla M: Preliminary prospective explanatory observation on the impact of 3-month steroid therapy on the objective measures of sleep-disordered breathing. Sleep Breath. 2012, 16:549-55. [10.1007/s11325-011-0541-x]

7. Ken-Dror G, Fry CH, Murray P, Fluck D, Han TS: Changes in cortisol levels by continuous positive airway pressure in patients with obstructive sleep apnoea: meta-analysis of 637 individuals. Clin Endocrinol (Oxf). 2021, 95:909-17. [10.1111/cen.14575]

8. Davies RJ, Ali NJ, Stradling JR: Neck circumference and other clinical features in the diagnosis of the obstructive sleep apnoea syndrome. Thorax. 1992, 47:101-5. [10.1136/thx.47.2.101]

9. Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J: Snoring and sleep apnoea in men: association with central obesity and hypertension. Int J Obes Relat Metab Disord. 1995, 17:533-40.