

## Original Article

# Sex Differences in Obstructive Sleep Apnea after Stroke

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**ABSTRACT: Background and Objectives:** Obstructive sleep apnea (OSA) is prevalent after stroke and associated with recurrent stroke, prolonged hospitalization, and decreased functional recovery. Sex differences in post-stroke OSA remain underexplored. The objective of this study was to evaluate sex differences in functional outcomes, stroke and OSA severity, and clinical manifestations of OSA in stroke patients with OSA. **Methods:** We retrospectively evaluated data from three previously conducted studies. Study patients had an imaging-confirmed stroke and had been found to have OSA (apnea-hypopnea index [AHI]  $\geq 5$ ) on either in-laboratory polysomnography or home sleep apnea testing performed within 1 year of their stroke. Linear regression models were used to evaluate study outcomes. **Results:** In total, 171 participants with post-stroke OSA (117 males [68.4%] and 54 females [31.6%]) were included. Female sex was an independent predictor for greater functional impairment ( $\beta = 0.37$ , 95% CI 0.029–0.71,  $p = 0.03$ ), increased stroke severity ( $\beta = 1.009$ , 95% CI 0.032–1.99,  $p = 0.04$ ), and greater post-stroke depressive symptoms ( $\beta = 3.73$ , 95% CI 0.16–7.29,  $p = 0.04$ ). Female sex was associated with lower OSA severity, as measured by the AHI ( $\beta = -5.93$ , 95% CI -11.21–-0.66). Sex was not an independent predictor of specific symptoms of OSA such as daytime sleepiness, snoring, tiredness, and observed apneas. **Conclusion:** Females with post-stroke OSA had poorer functional outcomes and more severe strokes compared to males, despite having lower OSA severity. Females with post-stroke OSA also exhibited more depressive symptoms. Understanding sex differences in patients with post-stroke OSA will likely facilitate better recognition of OSA and potentially improve clinical outcomes.

**RÉSUMÉ : L'apnée obstructive du sommeil après un accident vasculaire cérébral – Différences entre les sexes. Contexte et objectif :** L'apnée obstructive du sommeil (AOS) est fréquente après un accident vasculaire cérébral (AVC) et elle est associée à des récides d'AVC, à une hospitalisation prolongée et à un rétablissement moindre de la capacité fonctionnelle. Toutefois, il existe peu de données sur les différences, entre les sexes, quant à la présence d'AOS après un AVC. L'étude visait donc à évaluer les différences, entre les sexes, de résultats fonctionnels, de degré de gravité des AVC et de l'AOS, et de manifestations cliniques de l'AOS chez les patients ayant subi un AVC. **Méthode :** L'étude consistait en une évaluation rétrospective de données provenant de trois études antérieures. Dans tous les cas retenus, la présence de l'AVC avait été confirmée par des examens par imagerie, et la présence d'AOS (index apnées hypopnées [IAH]  $\geq 5$ ), par la polysomnographie en laboratoire ou par un test d'apnée du sommeil réalisé à domicile au cours de l'année écoulée depuis la survenue de l'AVC. Des modèles de régression linéaire ont servi à l'évaluation des résultats observés dans l'étude. **Résultats :** Ont été sélectionnés les dossiers de 171 participants souffrant d'AOS après un AVC (117 hommes [68,4 %] et 54 femmes [31,6 %]). Le sexe féminin s'est révélé un facteur prévisionnel indépendant de troubles fonctionnels plus importants ( $\beta = 0,37$ ; IC à 95 % : 0,029—0,71;  $p = 0,03$ ), d'un degré de gravité plus élevé des AVC ( $\beta = 1,009$ ; IC à 95 % : 0,032—1,99;  $p = 0,04$ ) et de symptômes de dépression plus marqués après un AVC ( $\beta = 3,73$ ; IC à 95 % : 0,16—7,29;  $p = 0,04$ ) que le sexe masculin. Par contre, le sexe féminin a été associé à un degré moindre de gravité de l'AOS sur l'échelle AHI ( $\beta = 5,93$ ; IC à 95 % : 11,21—0,66). Le sexe ne s'est pas révélé un facteur prévisionnel indépendant de certains symptômes de l'AOS, tels que la somnolence diurne, le ronflement, la fatigue et les épisodes d'apnée observés. **Conclusion :** Les femmes souffrant d'AOS après un AVC connaissaient une détérioration plus importante de la capacité fonctionnelle et un degré de gravité d'AVC plus élevé que les hommes, et ce, malgré un degré moindre de gravité de l'AOS. De plus, les femmes atteintes d'AOS après un AVC manifestaient des symptômes de dépression plus marqués. Aussi le fait de connaître les différences de résultats entre les sexes chez les patients atteints d'AOS après un AVC aura-t-il pour effet de faciliter la reconnaissance de l'AOS et, par suite, de mener potentiellement à de meilleurs résultats cliniques.

**Keywords:** Stroke; sleep; TIA

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## Introduction

Obstructive sleep apnea (OSA) is an important comorbidity that is seen in up to 70% of patients who have sustained a stroke (either ischemic or hemorrhagic stroke) or transient ischemic attack.<sup>1</sup> Despite the fact that untreated post-stroke OSA, which is defined as OSA that is diagnosed after one's stroke, is linked to increased length of hospitalization, recurrent vascular events, poorer functional recovery, impaired cognition, and decreased mood,<sup>2,3</sup> there is a paucity of literature that explores sex differences in this patient population. One study found that male sex was a predictor of post-stroke sleep disordered breathing,<sup>4</sup> and another study found that males with history of stroke had a greater severity of sleep disordered breathing compared to females with post-stroke sleep disordered breathing.<sup>5</sup> Otherwise, sex differences in post-stroke OSA remain underexplored.

Outside of the stroke literature, it has been demonstrated that females have less severe OSA compared to males.<sup>6</sup> In addition, females with OSA are less likely to experience classic OSA symptoms such as snoring and excessive daytime sleepiness compared to males but are more likely to report depression, difficulty falling asleep, and headache.<sup>7,8</sup> Previous studies have suggested that differences in upper airway anatomy, distribution of adiposity, control of ventilation, and hormonal status may account for the higher risk of OSA in males in the general population.<sup>9</sup> However, patients of both sexes with post-stroke OSA tend to differ in clinical presentation compared to patients with OSA without stroke. For example, stroke patients with OSA tend to have lower body mass indices (BMIs) and do not necessarily snore or experience significant daytime sleepiness compared to those with OSA but no stroke.<sup>10,11</sup>

There is a paucity of literature that explores sex differences in OSA after stroke. Accordingly, the purpose of this study was to explore sex differences in this patient population. Our primary objective was to examine sex differences in functional outcomes in patients with post-stroke OSA. We secondarily assessed sex differences in stroke severity, OSA severity, cognition, and clinical manifestations of post-stroke OSA.

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

We retrospectively evaluated data from three previously conducted studies,<sup>12–14</sup> all of which were approved by the local research ethics board. Written informed consent was obtained from all patients.

### Study Participants and Variables

Inclusion criteria for this study were: (1) stroke confirmed by a stroke physician on neuroimaging, and (2) a diagnostic in-laboratory polysomnography (PSG) or home sleep apnea test (HSAT) within 1 year of stroke demonstrating an apnea–hypopnea index (AHI)  $\geq 5$ . All participants from the three previously conducted studies underwent either level I, technologist-monitored in-laboratory PSG (Compumedics Neuroscan, Australia; scored according to the 2007 American Academy of Sleep Medicine criteria), or via HSAT using the ApneaLink Air, which is a level III portable sleep monitor. As per the 2007 American Academy of Sleep Medicine, recordings were manually scored by a sleep physician.<sup>15</sup> We excluded patients who declined undergoing either PSG or HSAT, or those with incomplete sleep data (defined as HSAT that captured less than 4 hours of data).

Sex, age, BMI, neck circumference, and presence of vascular risk factors were obtained. Post-stroke functional outcome was measured using the modified Rankin Scale (mRS).<sup>16</sup> Stroke severity was measured using the National Institutes of Health Stroke Scale score (NIHSS).<sup>17</sup> OSA severity, as assessed by the AHI, was obtained from either in-laboratory PSG or HSAT. The following questionnaires were administered to understand clinical manifestations of OSA: the Epworth Sleepiness Scale,<sup>18</sup> which assesses daytime sleepiness; the STOP-Bang questionnaire, which assesses the presence of OSA symptoms such as snoring, daytime fatigue, and observed apneas;<sup>19</sup> the Center for Epidemiologic Studies Depression Scale (CESD),<sup>20</sup> which measures self-reported symptoms associated with depression; and the Montreal Cognitive Assessment (MoCA),<sup>21</sup> which is a cognitive screening tool.

### Statistical Analysis

Descriptive variables were reported for the total sample and the male and female groups. Categorical variables were reported as frequency counts, and male and female groups were compared using chi-square tests. Normally distributed continuous variables were reported as means and standard deviations, and male and female groups were compared using independent sample *t* tests. Non-normally distributed continuous variables were reported as medians and interquartile ranges (IQRs), and male and female groups were compared using the Mann–Whitney *U* test.

Linear regression models were constructed to examine our primary hypothesis that sex would be independently associated with post-stroke functional status, as assessed by the mRS score. The linear regression model included the following covariates: sex, age, time between stroke and sleep study, AHI, and stroke severity. We also constructed linear regression models to evaluate our secondary hypothesis that sex would be independently associated with stroke severity (as measured by the NIHSS at the time of stroke). The covariates selected for this model were sex, age, AHI, and time between stroke and sleep study. We further constructed linear regression models to evaluate OSA severity (as assessed by the AHI derived from PSG or HSAT), cognition (as assessed by the MoCA), and OSA-related clinical features (e.g. daytime sleepiness [assessed by the ESS], depressive symptoms [assessed by the CESD], and items on the STOP-Bang questionnaire such as snoring, daytime fatigue, and observed apneas). These linear regression models used sex, age, time between stroke and sleep study, and stroke severity as covariates. Prior to modeling, all variables were assessed for multicollinearity (tolerance statistic value  $< 0.4$ ); if multicollinearity was found, only one variable of a correlated set was retained in the model. The final model was assessed for any potential violations to linear regression modeling using residual plots.

Statistics analyses were conducted using P.A.S.W Statistics 25.0 (SPSS Inc., Chicago, IL). Statistical significance was set at  $p < 0.05$ . As our secondary objectives were exploratory in nature, they were not corrected for multiple comparisons.

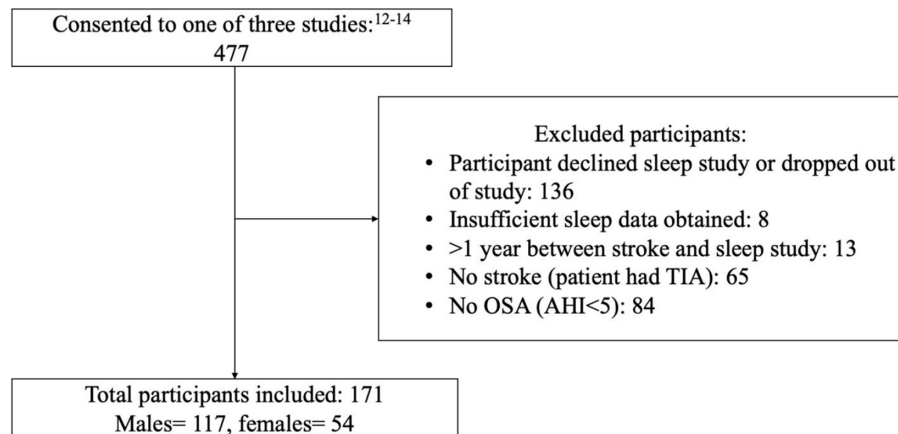
### Data Availability

Anonymized data may be available through a data transfer agreement in discussion with the corresponding author.

## Results

### Characteristics of the Study Population

A total of 171 participants were included in this study (Fig. 1). Of the total study population, 117 were male (68.4%) and 54 were

**Figure 1:** Participant breakdown.**Table 1:** Characteristics of study population

|  | All patients<br>(n = 171) | OSA (AHI ≥ 5) Males<br>(n = 117) | OSA (AHI ≥ 5) Females<br>(n = 54) | p     |
|--|---------------------------|----------------------------------|-----------------------------------|-------|
| Age – median (IQR) years   | 70.0 (17.0)               | 69.0 (16.0)                      | 72.5 (20.5)                       | 0.08  |
| Body mass index – median (IQR) kg/m <sup>2</sup>                   | 27.0 (6.0)                | 26.0 (6.0)                       | 27.5 (8.0)                        | 0.3   |
| Hypertension – n (%)   | 116 (67.8%)               | 80 (68.4%)                       | 36 (66.7%)                        | 0.8   |
| Dyslipidemia – n (%)   | 111 (64.9%)               | 79 (67.5%)                       | 32 (59.3%)                        | 0.3   |
| Diabetes – n (%)   | 48 (28.1%)                | 37 (31.6%)                       | 11 (20.4%)                        | 0.1   |
| Atrial fibrillation – n (%)  | 28 (16.4%)                | 17 (14.5%)                       | 11 (20.4%)                        | 0.3   |
| Current or prior smoker – n (%)                                    | 78 (45.6%)                | 59 (50.4%)                       | 19 (35.2%)                        | 0.06  |
| Prior stroke/transient ischemic attack – n (%)                     | 54 (31.6%)                | 35 (29.9%)                       | 19 (35.2%)                        | 0.5   |
| Modified Rankin Scale – median (IQR)                               | 1.0 (2.0)                 | 1.0 (1.0)                        | 1.0 (2.75)                        | 0.006 |
| NIH Stroke Scale – median (IQR)                                    | 1.0 (2.0)                 | 1.0 (2.0)                        | 1.0 (3.0)                         | 0.08  |
| Apnea–hypopnea index – median (IQR)                                | 15.0 (18.1)               | 17.0 (21.0)                      | 10.5 (14.0)                       | 0.03  |
| Apnea–hypopnea index severity                                      |                           |                                  |                                   |       |
| Mild (5–14) – n (%)  | 82 (48.0%)                | 48 (41.0%)                       | 34 (63.0%)                        | 0.007 |
| Moderate (15–29) – n (%)   | 51 (29.8%)                | 39 (33.3%)                       | 12 (22.2%)                        | 0.1   |
| Severe (≥30) – n (%)   | 38 (22.2%)                | 30 (25.6%)                       | 8 (14.8%)                         | 0.1   |
| Lowest oxygen desaturation – median (IQR) %                        | 83.0 (8.0)                | 83.0 (8.3)                       | 82.0 (7.0)                        | 0.8   |
| Centre for Epidemiological Studies Depression scale – median (IQR) | 11.0 (14.0)               | 9.0 (13.0)                       | 12.0 (18.0)                       | 0.8   |
| Epworth Sleepiness Scale score – median (IQR)                      | 7.0 (6.0)                 | 7.0 (6.0)                        | 6.0 (5.0)                         | 0.2   |
| STOP-Bang  | n = 155                   | n = 107                          | n = 48                            |       |
| Snoring – n (%)  | 37 (27.9%)                | 40 (37.4%)                       | 20 (41.7%)                        | 0.3   |
| Tiredness – n (%)  | 65 (41.9%)                | 43 (40.2%)                       | 22 (45.8%)                        | 0.5   |
| Observed apneas – n (%)  | 37 (23.9%)                | 25 (23.4%)                       | 12 (25.0%)                        | 0.9   |
| Montreal Cognitive Assessment – median (IQR)                       | 24.0 (7.0)                | 25.0 (7.0)                       | 23.0 (8.0)                        | 0.02  |

AHI = apnea–hypopnea index; IQR = interquartile range; NIH = National Institutes of Health; OSA = obstructive sleep apnea; STOP-Bang = snoring, tired, observed apneas, pressure, BMI, age, neck circumference, gender.

female (31.6%). Table 1 summarizes demographics, comorbidities, OSA severity, and mRS scores of participants. Sleep study was conducted at a mean of  $30 \pm 50$  days (median 5 days, IQR 31 days) post-stroke. Fifty-nine of the 171 enrolled participants completed PSG, and the remainder completed HSAT. Of the 59 participants who completed PSG, 15 (25.4%) were females.

### Linear Regression Analyses

For our primary objective, our linear regression model demonstrated that female sex ( $\beta = 0.37$ ,  $p = 0.03$ ), greater stroke severity ( $\beta = 0.29$ ,  $p < 0.01$ ), and increased time between stroke and sleep study ( $\beta = 0.003$ ,  $p = 0.03$ ) were significant independent predictors

**Table 2:** Linear regression multivariable models examining the relationship of sex with outcomes post-stroke in patients with OSA

| Independent predictors                                     | $\beta$ | $p$             | 95% CI        |
|--|---------|-----------------|---------------|
| <b>Modified Rankin Scale</b>                               |         |                 |               |
| Female sex (vs. male sex)                                  | 0.37    | <b>0.03</b>     | 0.029–0.71    |
| Age  | 0.006   | 0.32            | –0.006–0.017  |
| Apnea-hypopnea index                                       | 0.007   | 0.16            | –0.003–0.017  |
| NIH Stroke Scale   | 0.29    | <b>&lt;0.01</b> | 0.23–0.34     |
| Time between stroke and sleep study                        | 0.003   | <b>0.03</b>     | 0.001–0.007   |
| <b>NIH Stroke Scale</b>                                    |         |                 |               |
| Female sex (vs. male sex)                                  | 1.009   | <b>0.04</b>     | 0.032–1.99    |
| Age  | 0.008   | 0.63            | –0.025–0.042  |
| Apnea-hypopnea index                                       | 0.016   | 0.28            | –0.013–0.045  |
| Time between stroke and sleep study                        | –0.002  | 0.61            | –0.011–0.007  |
| <b>Center for Epidemiological Studies Depression Scale</b> |         |                 |               |
| Female sex (vs. male sex)                                  | 3.73    | <b>0.04</b>     | 0.16–7.29     |
| Age  | –0.15   | <b>0.01</b>     | –0.27– –0.034 |
| Apnea-hypopnea index                                       | 0.057   | 0.28            | –0.047–0.16   |
| NIH Stroke Scale   | 0.60    | <b>0.04</b>     | 0.044–1.16    |
| Time between stroke and sleep study                        | 0.037   | <b>0.03</b>     | 0.005–0.068   |
| <b>Montreal Cognitive Assessment</b>                       |         |                 |               |
| Female sex (vs. male sex)                                  | –1.73   | 0.05            | –3.46–0.005   |
| Age  | –0.042  | 0.16            | –0.100–0.016  |
| Apnea-hypopnea index                                       | –0.007  | 0.78            | –0.058–0.044  |
| NIH Stroke Scale   | –0.69   | <b>&lt;0.01</b> | –1.023– –0.36 |
| Time between stroke and sleep study                        | –0.005  | 0.49            | –0.020–0.010  |

OSA = obstructive sleep apnea; NIH = National Institutes of Health.

for a greater post-stroke mRS score (Table 2). When we used a linear regression model for mRS score using an interaction term between stroke severity and time between stroke and sleep study, we found that the time between stroke and sleep study did not influence the relationship between stroke and post-stroke mRS ( $\beta = 0.009$ ,  $p = 0.92$ ). Female sex ( $\beta = 0.13$ ,  $p = 0.038$ ) and stroke severity ( $\beta = 0.62$ ,  $p < 0.001$ ) were significant independent predictors of mRS in this model.

Female sex ( $\beta = 1.01$ ,  $p = 0.04$ ) was the only identified independent predictor for greater stroke severity as measured by the NIHSS. Female sex ( $\beta = 3.73$ ,  $p = 0.04$ ), younger age ( $\beta = -0.15$ ,  $p = 0.01$ ), increased stroke severity ( $\beta = 0.60$ ,  $p = 0.04$ ), and increased time between stroke and sleep study ( $\beta = 0.04$ ,  $p = 0.03$ ) were significant predictors of increased depressive symptoms, as measured by the CESD. Increased stroke severity ( $\beta = -0.69$ ,  $p < 0.01$ ) was a significant independent predictor of greater cognitive impairment, as measured by the MoCA. AHI, a marker of OSA severity, was not a significant predictor of neurological outcome, as measured by the mRS and NIHSS, depressive symptoms (CESD), cognition (MoCA), or daytime sleepiness (ESS) in our study population of stroke patients. There was no interaction between AHI and sex.

Table 3 includes linear regression model results for sleep variables. Male sex was the only significant independent predictor of increased OSA severity, as measured by the AHI ( $\beta = 5.93$ ,  $p = 0.03$ ). Sex was not a significant independent predictor for

**Table 3:** Linear regression multivariable models examining the relationship of sex with sleep variables in post-stroke OSA

| Independent predictors              | $\beta$ | $p$         | 95% CI        |
|-------------------------------------|---------|-------------|---------------|
| <b>Apnea-hypopnea index</b>         |         |             |               |
| Female sex (vs. male sex)           | –5.93   | <b>0.03</b> | –11.21– –0.66 |
| Age                                 | 0.14    | 0.14        | –0.044–0.32   |
| NIH Stroke Scale                    | 0.46    | 0.28        | –0.39–1.31    |
| Time between stroke and sleep study | –0.002  | 0.94        | –0.51–0.47    |
| <b>Epworth Sleepiness Scale</b>     |         |             |               |
| Female sex (vs. male sex)           | –1.031  | 0.22        | –2.68–0.62    |
| Age                                 | –0.011  | 0.71        | –0.067–0.045  |
| Apnea-hypopnea index                | 0.022   | 0.37        | –0.026–0.071  |
| NIH Stroke Scale                    | 0.15    | 0.25        | –0.11–0.42    |
| Time between stroke and sleep study | 0.006   | 0.42        | –0.009–0.021  |

OSA = obstructive sleep apnea; NIH = National Institutes of Health.

daytime sleepiness, as measured by the Epworth Sleepiness Scale ( $\beta = -1.03$ ,  $p = 0.22$ ). Finally, sex was not an independent predictor for individual components of the STOP-Bang questionnaire such as snoring, tiredness, and observed apneas (Table 4).



**Table 4:** Linear regression multivariable models examining the relationship of sex with items from the STOP-Bang questionnaire in post-stroke OSA

|                                     | Snoring                           | Tiredness                   | Observed apneas             |
|-------------------------------------|-----------------------------------|-----------------------------|-----------------------------|
| Independent predictors              | $\beta$ (95% CI), <i>p</i> -value |                             |                             |
| Female sex (vs. male sex)           | 0.13 (−0.058–0.31), 0.18          | 0.12 (−0.063–0.31), 0.19    | 0.012 (−0.15–0.17), 0.89    |
| Age                                 | −0.01 (−0.016– −0.004), <0.01     | −0.005 (−0.011–0.001), 0.14 | −0.006 (−0.011–0.001), 0.03 |
| Apnea–hypopnea index                | 0.006 (0.001–0.012), 0.03         | 0.004 (−0.001–0.010), 0.14  | 0.001 (−0.004–0.007), 0.60  |
| Time between stroke and sleep study | −0.001 (−0.002–0.001), 0.52       | 0.001 (0.001–0.003), 0.16   | −0.001 (−0.002–0.001), 0.35 |
| NIH Stroke Scale                    | −0.01 (−0.037–0.018), 0.49        | 0.006 (−0.022–0.034), 0.66  | 0.026 (0.002–0.051), 0.04   |

NIH = National Institutes of Health; OSA = obstructive sleep apnea; STOP-Bang = snoring, tired, observed apneas, pressure, BMI, age, neck circumference, gender.

## Discussion

In summary, our study found that females with OSA diagnosed after stroke had significantly greater functional impairment and stroke severity compared to males despite having less severe OSA. Females with post-stroke OSA also exhibited more depressive symptoms compared to males. There were no significant sex differences in presenting symptoms of OSA such as daytime sleepiness, as well as on individual items of the STOP-Bang questionnaire (i.e. snoring, tiredness, and observed apneas).

The literature suggests that stroke patients who have a diagnosis of OSA, regardless of their OSA severity, tend to have poorer functional recovery compared to stroke patients without OSA.<sup>22</sup> Our study builds upon the current literature by looking at sex differences in post-stroke OSA. We demonstrate that females with post-stroke OSA show poorer functional recovery compared to males with post-stroke OSA, despite males having more severe OSA compared to females. This relationship was found even after controlling for age, OSA severity, stroke severity, and timing of sleep test post-stroke. Besides female sex, other factors that were associated with increased functional impairment post-stroke included increased time of sleep study from stroke and increased stroke severity. Time between stroke and sleep study was evaluated in this study, given that literature suggests that OSA severity tends to decrease with more time from stroke.<sup>23</sup> However, timing of the sleep study was not found to be a significant contributor of sleep apnea severity in this population. This could be because participants were included if their sleep study was within 1 year of stroke. Interestingly, there was also no significant sex group differences in age, BMI, and presence of vascular risk factors that could potentially explain why females with post-stroke OSA had milder OSA but more functional impairment than males. This is unique from the general population, where differences have been documented in age, vascular risk factors, and BMI between males and females with OSA.<sup>24</sup> The lack of difference in a stroke population could suggest a unique relationship between stroke and OSA. This is also consistent with previous literature which suggested that traditional risk factors for OSA in a general population are not necessarily the same in stroke patients.<sup>5</sup>

The current literature also suggests that OSA is often misdiagnosed in females, and there is low prevalence of OSA among females compared to males.<sup>25</sup> This may, in part, be due to a proportionate lack of sleep study referrals for females.<sup>26</sup> OSA has generally been depicted as a disease of obese males. However, in the stroke population, it is well accepted that OSA manifests atypically.<sup>11</sup> In our study, females with post-stroke OSA exhibited significantly greater depressive symptoms, and there was a trend

toward females being more cognitively impaired compared to males. There is a risk that treating physicians may consider other possibilities such as post-stroke depression or cognitive impairment, rather than OSA, for nonspecific symptoms such as fatigue, and thereby potentially underdiagnose and undertreat women with OSA. Furthermore, previous studies in a non-stroke population have found that females are more likely to report symptoms of insomnia, morning headaches, and mood swings, which could result in underdiagnosis of OSA.<sup>27,28</sup> Insomnia symptoms may be endorsed, since the airway is most vulnerable to collapse during sleep–wake transition and can present as more awakenings at this time.<sup>24,27</sup> Therefore, this warrants more research in clinical tools to predict OSA in stroke patients, since typical symptoms of OSA such as those that are used on the STOP-Bang may not fully capture symptoms experienced by female stroke patients.

This study had a few limitations. One of the limitations is potentially the sample size. As previously noted, even though the HSAT used in this study has been validated against PSG, PSG remains the gold standard.<sup>29</sup> Also, we did not include participants with significant physical impairment, since they were generally unable to complete the study requirements. Therefore, our results may not be generalizable to patients with more severe strokes. Another limitation of this study was the lack of a control group with participants without OSA. Finally, a control group of patients who had not sustained a cerebrovascular event was not available for comparison. It would be difficult to make conclusions in a non-stroke population since our primary outcome, which was functional outcome measured by the mRS, and stroke severity, are not validated in non-stroke patients.

Overall, this study found that there were significant differences between males and females with post-stroke OSA in terms of functional outcomes, neurological deficits, and OSA severity. We postulate that this may be due to structural, hormonal, or other physiological differences between males and females, which may contribute to or be an explanation for why OSA manifests differently between the sexes. Current measures for sleep disordered breathing and respiratory physiology may also explain the sex differences we found in OSA severity. For example, females may have more frequent upper airway resistance and be less likely to have characteristic oxygen desaturation events, which are currently key to the diagnosis of sleep disordered breathing.<sup>30</sup> Hormonal differences may also drive such anatomical and physiological differences between males and females. It has been postulated that in a general population, incidence of OSA may also be associated with decreased sex hormones in postmenopausal

females and increased prevalence of hypothyroidism in females; however, more research is warranted in a stroke population.<sup>24,25</sup> Given that majority of females enrolled in this study with post-stroke OSA were of postmenopausal age range, this could suggest that closer screening for OSA in postmenopausal women with stroke may be beneficial in limiting underdiagnosis in female stroke patients.

Furthermore, given these known anatomical and physiological sex differences, there may need to be adjustments to the current diagnostic criteria used in OSA. For example, relies greatly on pulse oximetry, and since females are less likely to have large oxygen desaturations compared to males, the HSAT may underestimate overall AHI in females. Currently, OSA is typically diagnosed if an individual has an AHI greater than or equal to 5, and this is the same criteria used among both sexes. However, published normative PSG parameters in healthy adults have incorporated sex-related differences, such as an increase in the AHI by 0.2 for every 10% increase in the percentage of male participants.<sup>31</sup> These reference values suggest that clinicians should consider using different AHI cutoffs for females versus males when diagnosing OSA. The importance of sex differences when developing diagnostic criteria and cutoffs can be seen with acute coronary syndrome (ACS). Just like in OSA, women experiencing an ACS tend to present atypically compared to men. Based on the current literature, there is clinical value for the use of sex-specific cutoffs for the troponin, in that females should have a lower troponin cutoff compared to males due to physiological differences that result in females having a lower baseline troponin than males.<sup>32</sup> This same practice could be implemented when diagnosing OSA. More work is required in this area both in the general population and in the post-stroke OSA setting specifically.

## Conclusion

In a stroke population, females tend to have less severe OSA but greater neurological deficits and poorer functional outcomes compared to males. Understanding sex differences in patients with post-stroke OSA will likely facilitate better recognition of OSA and potentially improve clinical outcomes.

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