

SCIENTIFIC INVESTIGATIONS

## CPAP adherence is associated with reduced risk for stroke among older adult Medicare beneficiaries with obstructive sleep apnea

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**Study Objectives:** To examine the impact of adherence to continuous positive airway pressure (CPAP) therapy on risk of stroke among a nationally representative sample of older adults with obstructive sleep apnea.

**Methods:** We performed a retrospective cohort study among Medicare beneficiaries aged  $\geq 65$  years who were newly diagnosed with obstructive sleep apnea and had initiated CPAP (2009–2013). Monthly indicators of CPAP adherence included charges for machines, masks, or supplies and were summed over a 25-month follow-up to create a CPAP adherence variable. Stroke was modeled as a function of CPAP adherence using generalized estimating equations.

**Results:** We found that 5,757 beneficiaries met the inclusion criteria and were included in the final sample. Of these, 407 (7%) experienced stroke. After adjusting for demographic and clinical characteristics, CPAP adherence was associated with a reduced risk of stroke (hazard ratio, 0.98; 95% confidence interval, 0.96–0.99) over 25 months, indicating a 2% reduction in risk of stroke for each month of CPAP adherence. When sensitivity analyses were performed to stratify results by time since the first CPAP charge, the protective effect remained significant for the 12- and 6-month but not the 3-month outcome models.

**Conclusions:** In this national analysis of older adult Medicare beneficiaries with obstructive sleep apnea, CPAP adherence was associated with significantly reduced risk of stroke.

**Keywords:** obstructive sleep apnea, stroke, cardiovascular, continuous positive airway pressure, CPAP, treatment, adherence, Medicare, older adults

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### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Obstructive sleep apnea is a well-documented risk factor for stroke, including among older adults, but less is known about the potential protective effect of continuous positive airway pressure (CPAP) in reducing stroke in this population. The purpose of the current study was to evaluate the impact of CPAP adherence on the risk of stroke among a national sample of older adult Medicare beneficiaries.

**Study Impact:** In this national analysis of older adult Medicare beneficiaries with obstructive sleep apnea who initiated CPAP, CPAP adherence was associated with a small but significant reduction in stroke risk even after controlling for multiple demographic and disease comorbidity factors. These results show the importance of CPAP adherence in improving brain health and reducing the risk of stroke among older adults.

### INTRODUCTION

Obstructive sleep apnea (OSA) is common and costly in older adults.<sup>1</sup> In patients with OSA, the airway becomes partially or fully blocked during sleep, restricting oxygen supply to the brain and resulting in frequent cortical arousals. Untreated OSA increases the risk of cardiovascular diseases,<sup>2–5</sup> metabolic syndromes,<sup>6–8</sup> depression,<sup>9</sup> reduced quality of life,<sup>10</sup> and premature death<sup>11,12</sup> and dramatically increases health care utilization and costs.<sup>13–16</sup> Notably, OSA is a known risk factor for initial and repeat cerebrovascular events.<sup>17,18</sup> Stroke is the fifth leading cause of death and disability in the United States and worldwide.<sup>19</sup> Indeed, the prevalence of comorbid OSA among patients with stroke ranges from 50% to 70%<sup>5,20,21</sup> and is highest among older adults.

The most commonly prescribed and studied treatment for OSA is continuous positive airway pressure (CPAP) therapy. CPAP is associated with improved health outcomes in multiple domains.<sup>22</sup> Evidence has shown that CPAP can decrease mortality,<sup>23,24</sup> improve cognition,<sup>25</sup> and reduce hypertension<sup>26</sup> among older adults. Further, among older adults, CPAP is associated with improvements in multiple domains of daytime function, including reduced fatigue, sleepiness, and depression and increased quality of life.<sup>27</sup> Despite these benefits, many patients struggle to adjust to the therapy, resulting in suboptimal adherence comparable to adherence to treatment for other chronic diseases.<sup>28</sup> In a recent analysis of Medicare beneficiaries newly diagnosed with OSA, 74.9% (n = 2,417) met the 90-day Medicare CPAP adherence criteria, yet only 58.8% of these individuals (n = 1,420; 44% of those who initiated

CPAP) maintained possession of the CPAP machine throughout the 13-month rent-to-own period.<sup>29</sup> Thus, understanding the impact of CPAP adherence among this population is of paramount importance.

To date, very few studies have evaluated the impact of CPAP adherence on stroke among older adults with OSA.<sup>24,30,31</sup> This dearth of data is unfortunate as CPAP could potentially reduce the risk of stroke by reducing coagulability, systemic inflammation, blood pressure, and long-term vascular damage. Martínez-García and colleagues<sup>30</sup> conducted a prospective observational study among older adults ages  $\geq 65$  years ( $n = 939$ ) and found that compared with individuals without OSA, those with untreated mild-moderate OSA and treated OSA (any severity with CPAP  $> 4$  h/night) were not at increased risk of death because of stroke. Using the same cohort of older adults, Catalan-Serra and colleagues<sup>31</sup> reported that CPAP usage (mean adherence = 6.4 h/night) reduced the risk of stroke to levels comparable to those of patients without OSA or with untreated, mild-moderate OSA.

Despite these promising findings regarding CPAP adherence and stroke among older adults, the literature remains mixed. For example, McEvoy and colleagues<sup>32</sup> performed a large ( $n = 2,687$ ), well-publicized randomized clinical trial among middle-aged and older adults with pre-existing coronary or cerebrovascular disease ( $M = 61.3$  years; 81% male) and found no differences between participants randomized to CPAP and control patients (who used sham CPAP) in stroke outcomes. However, in a posthoc propensity score matched analysis, a beneficial effect of CPAP on stroke risk was observed.<sup>32</sup> Likewise, Schipper and colleagues<sup>33</sup> performed a prospective cohort study among adults (mean age =  $53.2 \pm 12.3$  years) ( $n = 554$ ) and found no relationship between self-reported CPAP adherence ( $> 4$  h/night) and incidence of stroke ( $P > .10$ ), although very few events were recorded. Another prospective cohort study conducted among older adults in China ( $n = 130$ ) found that relative to nonadherence, CPAP adherence ( $> 4$  h/night) was associated with a reduced risk of cardiovascular death (21.6% vs 5.6%;  $P = .04$ ), but risk reduction for stroke did not reach statistical significance.<sup>24</sup> Finally, Parra and colleagues<sup>34</sup> performed a relatively small randomized controlled trial (CPAP vs control) among older adults ( $n = 126$ ) with first-ever stroke. Over 5 years, CPAP did not significantly reduce the recurrence of stroke, although there was a nonsignificant increase in the control group. Stroke is a relatively rare event; thus, many of these prior studies were likely underpowered.

Given the high prevalence of OSA and cerebrovascular events among older adults, the known cerebrovascular risks associated with untreated OSA, and the potential beneficial but uncertain effect of CPAP on these cerebrovascular outcomes, it is somewhat surprising that few studies have evaluated the impact of CPAP adherence on cerebrovascular outcomes specifically among older adults.<sup>20</sup> Such insight would have direct clinical and policy relevance. To address this important gap in knowledge, the purpose of this population-level study was to examine the impact of CPAP adherence on cerebrovascular outcomes among a nationally representative sample of older adult Medicare beneficiaries. We hypothesized that CPAP

adherence would reduce the risk of cerebrovascular events including stroke.

## METHODS

### Data source and study population

We conducted a retrospective cohort study among Medicare beneficiaries aged  $\geq 65$  years and diagnosed with OSA who initiated CPAP using a 5% sample of Medicare administrative data for 2008–2015 obtained from the Centers for Medicare & Medicaid Services Chronic Condition Data Warehouse. The Chronic Condition Data Warehouse data are designed to facilitate research to improve the quality of care by linking beneficiaries across multiple files (eg, drug events, hospitalizations, and outpatient services) and providing extensive documentation on claim types, data use, and access.

OSA was defined as the presence of at least 1 OSA diagnosis between 2009 and 2013 (ie, inpatient or outpatient claims containing *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 780.51, 327.23, 780.57, or 780.53) and searched for at least 1 CPAP machine charge (ie, Healthcare Common Procedure Coding System code E0601) within 6 months of OSA diagnosis. Note that although the Centers for Medicare & Medicaid Services requires the apnea-hypopnea index to be calculated based on 4% desaturations, previous research has reported a minimal impact of the 4% apnea-hypopnea index rule on OSA diagnoses among older adults.<sup>35</sup> We required that no OSA, other sleep diagnoses, or CPAP charges had occurred during the 12 months before the first OSA diagnosis. To ensure the capture of CPAP charges and new stroke events, we required continuous Medicare Parts A, B, and D, with no Medicare Part C (Medicare Advantage) coverage for the 12 months before and the 24 months after the month of the first CPAP charge. Thus, all participants in the cohort survived for 24 months after the first CPAP charge.

### CPAP

To facilitate the capture of CPAP adherence, we relied on 2 criteria. The Centers for Medicare & Medicaid Services implemented objective adherence criteria required for reimbursement for CPAP beyond the first 3 months of use (ie,  $> 4$  h of CPAP on 70% of nights, or 21 days in a consecutive 30-day period within the first 90 days of CPAP initiation) in late 2008. Once these criteria are met, CPAP machines are billed over an additional 10 monthly (ie, 13 months total) payments during a “rent-to-own” period. Thus, we utilized the number of CPAP machine charges after the first CPAP charge as a proxy for CPAP adherence. Next, among beneficiaries with 13 CPAP charges, we looked for evidence of continued CPAP use over the following 12 months by searching for Healthcare Common Procedure Coding System codes representing CPAP masks and supplies (E0561, E0562, E0470, E0471, E0472, A7030, A7034, A7044, A7027, A7035, A7036, A7037, A4604, A7038, A7039, A7045, A7046, A7028, A7029, A7031, A7032, A7033, or E1399). At least 1 charge for a CPAP mask or other supply was considered evidence of continued CPAP use in all subsequent months until either the end of follow-up (25 months

**Table 1**—Baseline characteristics of Medicare beneficiaries ages  $\geq 65$  years and diagnosed with OSA 2009–2013 who received  $\geq 1$  CPAP fills by CV event status (n = 5,757).

	CV Event	No CV Event	P*
Age, y, mean (SD)	73.0 (5.9)	71.7 (5.3)	.001
Sex, n (%)			.08
Female	202 (50)	2,519 (46)	
Male	205 (50)	2,932 (55)	
Race, n (%)			.14
White, non-Hispanic	351 (86)	4,784 (89)	
Black, non-Hispanic	32 (8)	350 (6)	
Other	24 (6)	272 (5)	
Medicaid eligibility, n (%)	77 (19)	745 (14)	.006
OREC, n (%)			.13
Age	357 (88)	4,819 (90)	
Other	50 (12)	531 (10)	
Comorbidities, n (%)			
ADRD	35 (9)	260 (5)	.001
Anemia	209 (51)	2,186 (41)	< .001
Atrial fibrillation	101 (25)	899 (17)	< .001
Cataracts	289 (71)	3,218 (60)	< .001
Chronic kidney disease	115 (28)	940 (18)	< .001
COPD	129 (32)	1,286 (24)	< .001
Depression	101 (25)	1,154 (22)	.13
Diabetes	196 (48)	2,185 (41)	.004
Gout	15 (4)	148 (3)	.28
Heart failure	180 (44)	1,400 (26)	< .001
Hyperlipidemia	362 (89)	4,413 (82)	< .001
Hypertension	384 (94)	4,578 (86)	< .001
Ischemic heart disease	267 (66)	2,787 (52)	< .001
Obesity	46 (11)	519 (10)	.30
Osteoporosis	101 (25)	1,114 (21)	.06
Rheumatoid arthritis	240 (59)	2,761 (52)	.004

\*P value from chi-square goodness-of-fit test or Student t test. ADRD = Alzheimer disease and related dementias, COPD = chronic obstructive pulmonary disease, CPAP = continuous positive airway pressure, CV = cerebrovascular, OREC = original reason for entitlement, OSA = obstructive sleep apnea, SD = standard deviation.

maximum, counting the month of the first CPAP charge) or the first cerebrovascular event. Finally, we operationalized adherence to CPAP as the number of months of CPAP use. This value either changed monthly with continued CPAP use or remained at a constant value, representing the total number of months with evidence of CPAP use among those who stopped using CPAP. Thus, the adherence variable had a range of 1–25. To ensure temporality between the CPAP adherence variable and stroke events, the adherence variable was lagged by 1 month.

## Stroke

Our primary outcome was an ischemic stroke after the first CPAP charge (ie, *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 436, 435.9, 434.91, 434.11, 434.01, 433.01, 433.11, 433.21, 433.91, 433.81, V12.54, 438.1 $\times$ , 438.2 $\times$ , 438.3 $\times$ , 438.4 $\times$ , 438.5 $\times$ , 438.8 $\times$ , or

438.9) and before the end of follow-up. Hemorrhagic stroke was excluded. We used the date of the new stroke event to create a time-varying monthly indicator. We excluded beneficiaries with a history of stroke before the first CPAP charge.

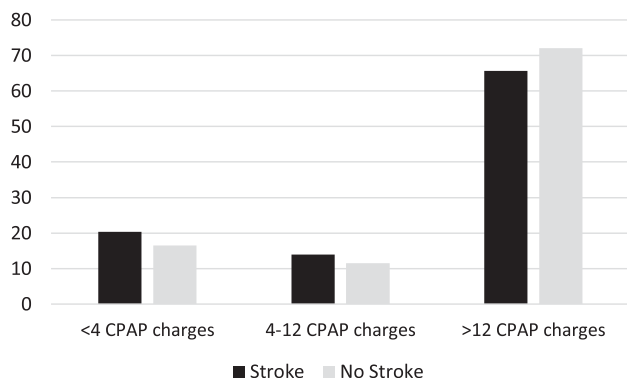
## Covariates

The Chronic Condition Data Warehouse contains information on 27 comorbid conditions and 40 other chronic or potentially disabling conditions, with an annual flag for each condition and date of first diagnosis.<sup>36</sup> We used the date of first diagnosis to determine whether a condition was present at the first CPAP charge (ie, index date).

## Data analysis

We assessed the distribution and frequencies of all variables. We calculated the proportion of beneficiaries who fell into each

**Figure 1**—Percentage of Medicare beneficiaries with OSA (2009–2013) with and without new stroke events, by CPAP adherence category (n = 5,757).



CPAP = continuous positive airway pressure, OSA = obstructive sleep apnea.

CPAP adherence category (< 4, 4–12, and > 12 CPAP charges) by outcome status at the end of follow-up and displayed this graphically. We assessed differences in the distribution of demographic and clinical variables by outcomes status using the chi-square goodness-of-fit test and the Student *t* test.

To model the effect of CPAP adherence on the risk of stroke, we used generalized estimating equations with a binary distribution and complementary log-log link (discrete time model).<sup>37</sup> Individuals were censored after the first stroke or at the end of the 25-month follow-up. First, we modeled the association between the lagged adherence to the CPAP variable and risk of stroke, adjusting for time since the OSA diagnosis. Next, we added covariates known to be associated with the outcome from a bivariate analysis (Table 1) to the model, keeping those whose *P* value remained < .05.

Time was correlated with reduced risk of stroke and with CPAP duration. Thus, we stratified our analyses by time since the first CPAP charge: 3 months, 6 months, 12 months, and 25 months. CPAP duration within each stratum could not be greater than the number of months since the first CPAP charge. Model-building proceeded as described in the above paragraph. We report hazard ratios (HR) and 95% confidence intervals (CI). To determine whether the effect of cumulative CPAP use on the risk of stroke differed among subpopulations, we tested effect modification by dual-eligibility status (ie, Medicare/Medicaid), race, (ie, White non-Hispanic, Black non-Hispanic, and other), and sex by including interaction terms in the regression model one at a time and evaluating the Wald chi-square *P* value. Statistical significance was set at *P* < .05.

Analyses were performed with SAS Studio version 3.71 (SAS Institute, Cary, NC). This study was approved by the institutional review board of the University of Maryland, Baltimore.

## RESULTS

We identified 5,757 Medicare beneficiaries diagnosed with OSA between 2009 and 2013 who initiated CPAP therapy and

met the inclusion criteria. The mean age was 71.8 years (standard deviation, 5.3 years) and 46% were female (Table 1). At the time of the first CPAP charges, the cohort had a high prevalence of comorbidities. For example, the prevalence of diabetes was 41%, that of ischemic heart disease was 53%, and that of hypertension was 86%. Subsequently, 407 (7%) of the overall cohort experienced a stroke during the follow-up period.

Figure 1 displays the percentage of beneficiaries with and without new stroke events within each CPAP adherence category. Among individuals who did not experience a stroke, 72% had > 12 CPAP charges, whereas only 65.6% of those who experienced a stroke had > 12 CPAP charges. In unadjusted models for the full 25-month follow-up, the lagged duration of CPAP use was associated with a reduction in the risk of stroke (HR, 0.98; 95% CI, 0.96–0.99; Table 2). After adjustment for demographic and clinical characteristics, the lagged duration of CPAP use remained associated with a significant reduction in the risk of stroke (HR, 0.98; 95% CI, 0.97–1.00; *P* = .02). Thus, for every additional month of CPAP use, an additional 2% reduction in the relative risk of stroke was observed. After adjustment, we observed a similar protective effect of lagged CPAP duration on the risk of stroke at 12 months since the first CPAP charge (HR, 0.96; 95% CI, 0.92–0.99; *P* = .02) and at 6 months since the first CPAP charge (HR, 0.85; 95% CI, 0.77–0.93; *P* < .001). At 3 months since the first CPAP charge, we observed a protective effect, but it was not statistically significant (HR, 0.91; 95% CI, 0.76–1.09; *P* = .29). We observed no effect modification by dual-eligibility status, race, or sex.

## DISCUSSION

In this national study of older adult Medicare beneficiaries with OSA, CPAP adherence was associated with a small but significant reduction in the risk of stroke over 25 months. This protective effect of CPAP adherence remained statistically significant even after controlling for demographic characteristics and for medical and psychiatric comorbidities. Not only do these results represent the largest analysis of CPAP adherence and stroke outcomes among older adults to date, but this study also provides a population health perspective highlighting the importance of CPAP adherence as a modifiable factor to improve cerebrovascular health among older adult Medicare beneficiaries.

The most important finding from this study is that each additional month of CPAP adherence was associated with a reduced risk of stroke among older adults, over 6, 12, and 25 months of follow-up. Results remained significant even after controlling for demographic characteristics and medical comorbidities. A lack of significant results at the 3-month follow-up may be explained by 2 factors. First, because the CPAP duration variable was lagged, there were only 2 possible levels of CPAP use at 3 months: 1 month and 2 months. Second, the smaller number of stroke events within 3 months may have reduced power to detect a statistically significant effect, even though the observed effect was in fact protective.

Consistent with a recent analysis of CPAP adherence and cardiovascular disease,<sup>38</sup> the present results provide further



**Table 2**—Association between lagged monthly duration of CPAP use and risk of new CV events among Medicare beneficiaries with OSA, stratified by time since first CPAP fill.

Lagged Monthly Duration of CPAP Use	25-Month Outcome (407 events)	12-Month Outcome (246 events)	6-Month Outcome (138 events)	3-Month Outcome (99 events)
Unadjusted	0.98 (0.96–0.99)	0.95 (0.92–0.99)	0.84 (0.77–0.93)	0.90 (0.75–1.08)
Adjusted*	0.98 (0.97–1.00)**	0.96 (0.92–0.99)	0.85 (0.77–0.93)	0.91 (0.76–1.09)

Values are presented as unadjusted and adjusted HRs (95% CI). \*25-month outcome model adjusted for cataracts, congestive heart failure, chronic kidney disease, hypertension; 12-month outcome model adjusted for age, congestive heart failure, chronic kidney disease; 6-month outcome model adjusted for age, congestive heart failure; 3-month outcome model adjusted for age, atrial fibrillation, chronic kidney disease. \*\* $P = .02$ . CI = confidence interval, CPAP = continuous positive airway pressure, CV = cerebrovascular, HR = hazard ratio, OSA = obstructive sleep apnea.

empirical support for the health benefit of CPAP adherence among older adults. Because of the potentially devastating nature of stroke, even the relatively small reduction in risk observed in this study (ie, 2% reduction per month over 25 months) represents a potentially important clinical and public health priority. Notably, the pattern of protective results remained constant across racial, sex, and socioeconomic subgroups of Medicare beneficiaries. This is the first study to examine the protective effect of CPAP adherence on cerebrovascular risk across health disparity subgroups. A recent study reported that lower socioeconomic status is associated with reduced CPAP adherence among older adults,<sup>29</sup> and a majority of studies have found that relative to White individuals, members of racial minority subgroups are less adherent to CPAP.<sup>39</sup> The present results highlight the importance of achieving CPAP adherence among all health disparity populations. More broadly, the current findings support the tailoring of evidence-based CPAP adherence interventions (eg, cognitive-behavioral and motivational approaches<sup>22</sup>) for use in older adults.

Finally, among this national sample of older adults with OSA, the prevalence of comorbid disease was notably high, including comorbid diabetes (41%), ischemic heart disease (53%), and hypertension (86%). By contrast, the prevalence of these conditions was approximately 40% lower (eg, ischemic heart disease ~31%<sup>40</sup>) in the overall Chronic Condition Data Warehouse data during the same years.<sup>40</sup> These results suggest that OSA comorbidity and multimorbidity warrant further research attention.

Our study possesses strengths. First, unlike many prior studies, our large population sample ensured adequate statistical power to evaluate incident ischemic stroke. Prior studies of CPAP and stroke among older adults have generally been smaller; even the relatively large SAVE trial was underpowered to consider stroke as a stand-alone hard outcome. Second, in addition to being large, our sample was selected from a nationally representative sample of Medicare administrative claims data, ensuring a high degree of generalizability to most older adults in the United States. Third, also related to our sample, the inclusion criteria required not only a new diagnosis of OSA but also the initiation of CPAP therapy, thus ensuring a high degree of specificity for OSA. Finally, we employed a conservative definition of CPAP adherence, assessing both machine charges during the 13-month rent-to-own period and resupply charges during subsequent months of follow-up. To

ensure temporality between the adherence measure and stroke events, the CPAP adherence variable was also lagged.

At the same time, our study has limitations. Most important, our administrative methodology precluded the assessment of important potential confounders, such as OSA disease severity, other sleep characteristics, daytime symptoms, and other factors influencing cerebrovascular events and stroke. Second, because we used CPAP machine and resupply charges as a proxy for objective CPAP adherence, we were unable to evaluate the dose-response relationship between hours of nightly CPAP use and stroke outcomes. Even so, our approach to leveraging Medicare claims data to examine the impact of CPAP adherence was based on Medicare policy (90-day adherence criteria requiring physician confirmation of objective device usage and symptomatic improvement) and past literature.<sup>29,41</sup> We were not able to adjust for concurrent medications, which could have been confounders if they were associated with both adherence to CPAP and risk of stroke. Finally, we observed important differences in the comorbidity burden associated with CPAP adherence. To address this concern, we controlled for baseline stroke, demographic characteristics, and all disease comorbidities. Despite our best efforts to reduce residual confounding, it is possible that residual confounding persisted between groups.

## CONCLUSIONS

This national study represents the largest analysis of the impact of CPAP adherence on cerebrovascular outcomes and stroke among older adults to date. For each month of CPAP use, a reduction in stroke risk was observed. This pattern of results was consistent across all racial, sex, and low-socioeconomic status subgroups of Medicare beneficiaries. Given the massive public health burden associated with cerebrovascular diseases and stroke, multiple stakeholders including patients, payors, policy makers, and health providers should seek to increase awareness and maximize CPAP adherence among older adults with OSA.

## ABBREVIATIONS

CI, confidence interval  
 CPAP, continuous positive airway pressure  
 HR, hazard ratio  
 OSA, obstructive sleep apnea

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