


# Sleep-Disordered Breathing and Poststroke Outcomes

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**Objective:** To examine the association between sleep-disordered breathing and stroke outcomes, and determine the contribution of sleep-disordered breathing to outcome disparities in Mexican Americans.

**Methods:** Ischemic stroke patients ( $n = 995$ ), identified from the population-based Brain Attack Surveillance in Corpus Christi Project (2010–2015), were offered participation in a sleep-disordered breathing study including a home sleep apnea test (ApneaLink Plus). Sleep-disordered breathing (respiratory event index  $\geq 10$ ) was determined soon after stroke. Neurologic, functional, cognitive, and quality of life outcomes were assessed at 90 days poststroke. Regression models were used to assess associations between sleep-disordered breathing and outcomes, adjusted for sociodemographics, prestroke function and cognition, health-risk behaviors, stroke severity, and vascular risk factors.

**Results:** Median age was 67 years (interquartile range [IQR] = 59–78); 62.1% were Mexican American. Median respiratory event index was 14 (IQR = 6–25); 62.8% had sleep-disordered breathing. Sleep-disordered breathing was associated with worse functional outcome (mean difference in activities of daily living/instrumental activities of daily living score = 0.15, 95% confidence interval [CI] = 0.01–0.28) and cognitive outcome (mean difference in modified Mini-Mental State Examination =  $-2.66$ , 95% CI =  $-4.85$  to  $-0.47$ ) but not neurologic or quality of life outcomes. Sleep-disordered breathing accounted for 9 to 10% of ethnic differences in functional and cognitive outcome and was associated with cognitive outcome more strongly for Mexican Americans ( $\beta = -3.97$ , 95% CI =  $-6.63$  to  $-1.31$ ) than non-Hispanic whites ( $\beta = -0.40$ , 95% CI =  $-4.18$  to  $3.39$ ,  $p$ -interaction = 0.15).

**Interpretation:** Sleep-disordered breathing is associated with worse functional and cognitive function at 90 days poststroke. These outcomes are reasonable endpoints for future trials of sleep-disordered breathing treatment in stroke. If effective, sleep-disordered breathing treatment may somewhat lessen ethnic stroke outcome disparities.

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Stroke is the fifth leading cause of death in the United States.<sup>1</sup> Stroke mortality rates have declined substantially over the past 4 decades.<sup>2</sup> Decreasing stroke mortality in combination with aging of the US population will result in an increase in the number of people living with stroke-related disability. Projections suggest that by 2050 the number of stroke events will reach 1.3 million, with the greatest increases in minority populations, who have higher stroke rates, worse stroke outcomes, and greater projected population growth.<sup>3</sup> The increase in the number of disabled stroke survivors will pose significant challenges to the US

health care system, pointing to the urgent need for new interventions to improve stroke recovery.

Sleep-disordered breathing (SDB), a treatable condition, is highly prevalent in ischemic stroke patients.<sup>4</sup> The limited epidemiologic data on the association between SDB and stroke outcomes have come primarily from small, single-hospital or rehabilitation-based studies.<sup>5–15</sup> Patients in inpatient rehabilitation are a select group of moderately severe stroke patients who are medically stable enough to participate in more lengthy therapy sessions. Thus, stroke patients with more adverse outcomes, and possibly more severe SDB, are

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excluded, introducing possible selection bias. Data from larger, population-based studies that represent the broader stroke population are lacking. Moreover, information is limited on the impact of SDB on stroke outcomes beyond disability, such as quality of life (QOL) and cognition.

Small randomized clinical trials (RCTs) have demonstrated that treatment of SDB with continuous positive airway pressure (CPAP) in select groups of stroke/transient ischemic attack (TIA) patients may improve functional outcome, cognitive outcome, neurologic recovery, and depressive symptoms, although results have not been conclusive.<sup>16–25</sup> If treatment with CPAP is shown to improve stroke outcomes in a larger, adequately powered clinical trial, treatment of SDB may be a viable, cost-efficient intervention strategy to improve stroke recovery. Observational data on the association of SDB with a variety of stroke outcomes could inform the most appropriate endpoints for future recovery trials of SDB treatment in stroke patients.

Minority populations, including Mexican Americans (MAs), in comparison to non-Hispanic whites (NHWs), have worse poststroke outcomes and a higher prevalence of post-ischemic stroke SDB.<sup>4,26</sup> If SDB is associated with worse outcomes, then SDB may contribute to ethnic stroke outcome disparities and through its treatment offer a novel opportunity to reduce disparities. In addition, the association between SDB and stroke outcomes may vary by ethnicity due to ethnic differences in the pathophysiology of SDB. Data on the association between SDB and stroke outcomes from diverse populations, who bear a greater stroke burden, are lacking.

The objectives of this study therefore were 2-fold: (1) to examine the association between SDB and 90-day stroke outcomes, and (2) to understand the contribution of SDB to worse stroke outcomes in MAs compared with NHWs.

## Patients and Methods

### Study Setting

The ongoing Brain Attack Surveillance in Corpus Christi (BASIC) Project takes place in Nueces County, Texas, which had a population of 361,350 in 2016, the majority being US-born MAs.<sup>27</sup> Nueces County is similar to other US communities with high concentrations of US-born MAs with respect to sociodemographic factors linked to stroke, suggesting results will be generalizable to the non-immigrant US MA population.<sup>28</sup> The county has 7 acute care hospitals, with other major referral centers ~150 miles away, affording complete case capture for acute stroke.

### Stroke Ascertainment

Detailed methods of the BASIC Project have been published.<sup>29</sup> Briefly, active and passive surveillance methods are used to identify possible strokes at all hospitals in the

study area. Active surveillance entails routinely screening hospital admission logs for screening terms suggestive of stroke as well as routinely canvassing hospital floors and intensive care units for in-hospital strokes. Passive surveillance entails review of discharge diagnosis codes for stroke. All possible strokes are validated by stroke fellowship-trained physicians blinded to ethnicity and age. This analysis was focused on ischemic strokes defined using a standard clinical definition.<sup>30</sup> Only patients who were MAs or NHWs were included due to the small numbers for other racial-ethnic groups.

### Sleep-Disordered Breathing

Individuals are approached soon after stroke for participation in BASIC, which includes a baseline interview and an outcome interview at ~90 days after stroke. Eligibility includes age  $\geq 45$  years, residence in Nueces County for  $\geq 6$  months per year, and stroke not as a result of trauma. Individuals are eligible for the SDB portion of the study if stroke onset is within 30 days if it is identified through active surveillance, and within 45 days if it is identified through passive surveillance. Exclusion criteria include current pregnancy or use of oxygen or positive pressure ventilation. Eligible individuals are offered participation in an SDB study that includes a home sleep apnea test (HSAT) with the well-validated ApneaLink Plus.<sup>31</sup> A recent study supported the accuracy of poststroke SDB assessment with an HSAT.<sup>32</sup> Trained study coordinators apply the device in the hospital or the subjects' homes. Raw data are downloaded for processing by the ApneaLink software. Default settings for the software are used for automated scoring, with edits to start and stop times and artifacts by a registered polysomnographic technologist. As previously detailed,<sup>33</sup> the technologist also adjusts poor quality data, reactivates some data for scoring through sensitivity adjustment, and reclassifies a small number of apneic events not scored in a manner consistent with guidelines. Definitions for apneas and hypopneas were as follows: *apneas*, a decrease in nasal pressure of  $\geq 80\%$  from baseline for  $\geq 10$  seconds; *hypopneas*, a decrease in nasal pressure of  $\geq 30\%$  compared to baseline, lasting  $\geq 10$  seconds and associated with a  $\geq 4\%$  oxygen desaturation. In the presence of missing oximetry data, hypopneas were defined as a reduction in nasal pressure of  $\geq 50\%$  for  $\geq 10$  seconds. A respiratory event index (REI), the sum of apneas plus hypopneas per hour of recording, was calculated. SDB was identified by an REI  $\geq 10$ . Although the International Classification of Sleep Disorders defines significant obstructive sleep apnea by an apnea-hypopnea index or REI  $\geq 5$ , we chose the higher threshold (and a focus on "significant SDB") a priori in view of the high sensitivity and specificity for the ApneaLink at this cutpoint, and our evidence that nearly all poststroke patients might qualify for SDB if the lower

threshold were used.<sup>4,31</sup> ApneaLink Plus results were provided to subjects after their 90-day outcome assessment.

### Stroke Outcomes

In-person interviews are conducted with subjects or their proxy (if subject is unable to communicate) at ~90 days following stroke. Neurologic outcome measured by the National Institutes of Health Stroke Scale (NIHSS) is assessed by certified study coordinators. Functional outcome is measured with 7 self-reported activities of daily living (ADL) and 15 instrumental activities of daily living (IADL). Subjects respond to their level of difficulty performing each ADL/IADL item with a Likert scale ranging from 1 (no difficulty) to 4 (can only do with help). The items are averaged to create a functional outcome score ranging from 1 to 4, with higher scores representing worse function. Cognitive outcome is measured with the modified Mini-Mental State Examination (3MSE). The 3MSE ranges from 0 to 100, with higher scores representing better cognitive function. Subjects are administered a series of questions to assess language dysfunction and ability to participate in cognitive testing prior to administration. QOL is measured with the short form Stroke Specific Quality of Life (SS-QOL) scale, which has been validated in our population.<sup>34</sup> The SS-QOL ranges from 1 to 5, with higher scores representing better QOL. All-cause mortality is ascertained through records from the Texas Department of State Health Services and next of kin reports.

### Covariates

Potential confounders included sociodemographic and prestroke characteristics from baseline interviews and stroke characteristics and vascular risk factors from medical records. Sociodemographic characteristics were race–ethnicity, age, sex, education, and marital status. Prestroke characteristics included cognitive impairment measured by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; categorized as normal cognitive function, cognitive impairment without dementia, dementia),<sup>35</sup> functional disability measured by the modified Rankin Scale (mRS; categorized as no, slight/moderate, severe), and health-risk behaviors (current smoking, alcohol use in 4 categories). Stroke characteristics included initial stroke severity measured by the NIHSS and intravenous tissue plasminogen activator (tPA) use. Vascular risk factors included body mass index, atrial fibrillation, diabetes, coronary artery disease, history of stroke/TIA, hypertension, and hyperlipidemia.

BASIC was approved by the institutional review boards at the University of Michigan and the local hospital systems. All patients or their surrogates provided written informed consent.

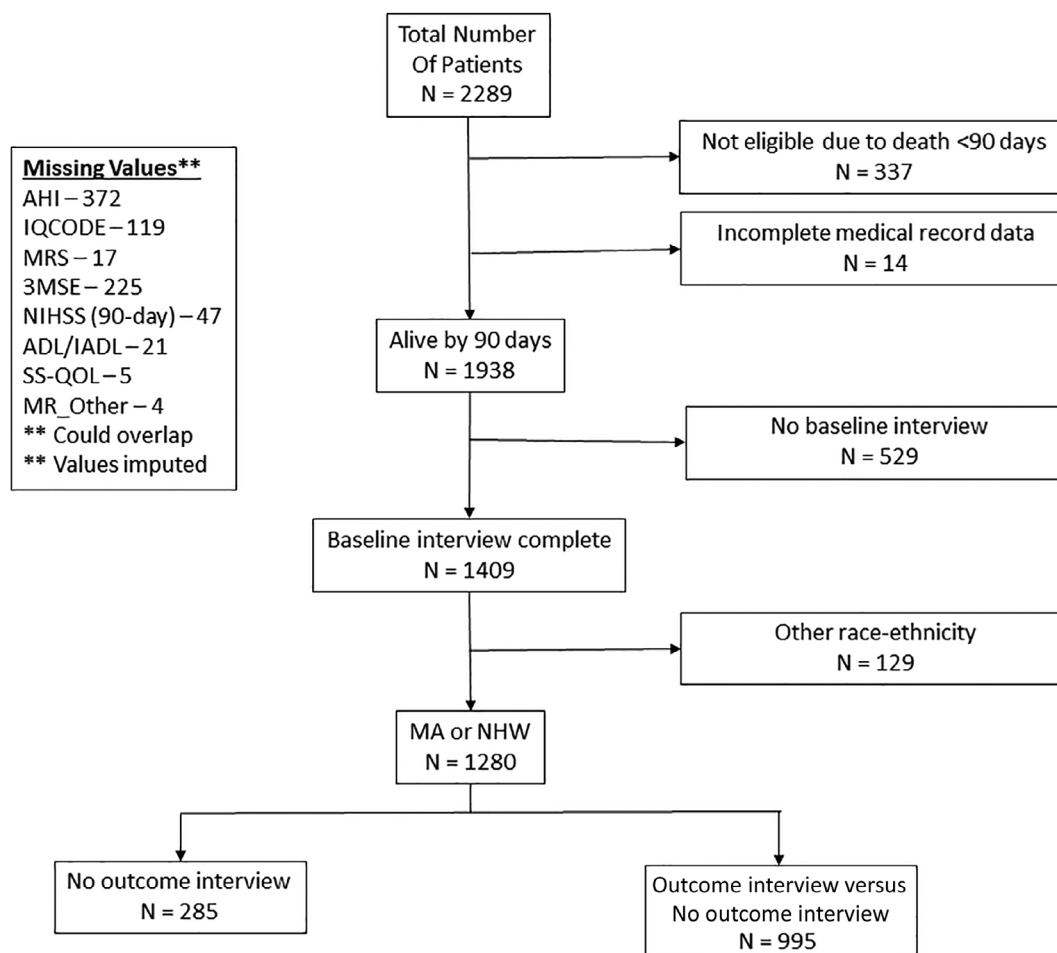
### Study Participants

Sample construction and attrition are presented in the Figure 1. Briefly, there were 2,289 ischemic stroke patients identified (August 23, 2010 to December 29, 2015). For patients who experienced >1 event during the study period, the first event with SDB testing was retained. Among the 2,289 patients, 337 patients who died prior to 90 days and 14 patients who had incomplete medical record data were excluded. Among the remaining 1,938 patients, 1,280 MA and NHW patients participated in the baseline interview, of whom 995 had a 90-day outcome interview. Of the 995 with outcome data, 623 had SDB measured. Missing values for SDB (n = 372), IQCODE (n = 119), and other covariates were multiply imputed using a regression predictive matching algorithm. Outcome models for the primary analysis were fit in the 995 patients. Data for patients who remained alive but did not participate in the baseline interview (n = 337), and those who participated in a baseline but not outcome interview (n = 285), were used in analysis to account for any potential differential attrition using inverse probability weighting but were not included in the primary analysis. Descriptive analyses comparing those who did and did not participate in the baseline interview and those who did and did not participate in the sleep study are presented in Supplementary Tables 1 and 2.

### Statistical Analysis

Differences in sample characteristics by participation status were examined using chi-squared and *t* tests. Logistic regression models were used to derive inverse probability weights (IPWs) to account for differential participation at baseline, and attrition from baseline to the 90-day outcome assessment.<sup>36</sup> Weights were calculated as the inverse of the probability of participation at baseline (weight 1) and the inverse probability of participation in outcome given baseline participation (weight 2). Each weight was stabilized by multiplying it by the average probability of participation at each stage, and trimmed at the 1st and 99th percentiles of the distribution to minimize the impact of extreme weights. The 2 weights were multiplied together to produce a final weight to be used in regression models.

Weighted regression models were used to investigate the adjusted associations between SDB and 90-day outcomes. As cognitive, functional, and QOL scores exhibit truncated distributions, we used Tobit regression for these outcomes. Robust regression was used to model log-transformed NIHSS measured at 90 days to accommodate the skewed distribution of this outcome. We estimated separate models for each outcome, adjusted for sociodemographics (age, sex, ethnicity, education, marital status), prestroke functional disability (mRS) and cognitive impairment (IQCODE), health-risk behaviors (alcohol intake and smoking), initial NIHSS, treatment with tPA, and vascular risk factors (body mass index,



**FIGURE 1:** Sample construction and attrition. 3MSE = modified Mini-Mental State Examination; ADL = activities of daily living; AHI = apnea-hypopnea index; IADL = instrumental activities of daily living; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; MA = Mexican American; MR\_Other = missing race\_ethnicity; MRS = modified Rankin Scale; NHW = non-Hispanic white; NIHSS = National Institutes of Health Stroke Scale; SS-QOL = Stroke Specific Quality of Life.

atrial fibrillation, coronary artery disease, diabetes, hypertension, high cholesterol, history of stroke/TIA). Body mass index was modeled continuously including a quadratic term to accommodate lack of linearity.

To examine the role of SDB in ethnic disparities, we investigated both the potential for SDB to confound the ethnicity–outcome associations and differences in SDB–outcome associations by ethnicity. Although it is possible that SDB serves as a mediator between ethnicity and stroke outcomes through a genetic mechanism,<sup>37</sup> we hypothesize that the more likely scenario is an association between ethnicity and SDB due to environmental and lifestyle factors. Thus, we focus our analysis, and interpretation of the role of SDB in ethnic stroke outcome disparities, on confounding versus mediation. For confounding, we estimated ethnic differences with and without inclusion of SDB in the confounder-adjusted models. For effect modification, we included interaction terms between ethnicity and SDB, and between ethnicity and all other covariates. This strategy approximates stratified models by ethnicity, but has the advantage of formally testing

for differences in the association of SDB and outcome by ethnicity. A priori, a  $p$  value of 0.15 was set to determine presence of effect modification.<sup>38</sup> We report ethnic-specific associations between SDB and outcomes from stratified models for ease of interpretation.

To estimate the proportion of the outcomes in the stroke population attributable to SDB, we calculated ethnic-specific estimates of population attributable risk percentage (PAR%). This analysis was limited to cognitive outcome, as this outcome had a significant association with SDB in MAs. For these calculations, a separate fully adjusted logistic regression model was run to estimate the relative risk for poor outcome associated with SDB, with poor outcome defined as 3MSE < 78.<sup>39</sup>

## Results

Tables 1 and 2 includes participant characteristics in the complete data ( $n = 995$ ) as well as in the imputed data. Median age was 67 years (interquartile range [IQR] = 59–78), 62.1% were MAs, and 51.7% were women. Median REI was

**TABLE 1. Baseline Characteristics for Complete and Imputed Data**

Variable	n	Complete Data Median (IQR) or %	Imputed Data, n = 995, Median (IQR) or %
Sociodemographic characteristics			
Mexican American	995	62.1	62.1
Female	995	51.7	51.7
Age	995	67.0 (59.0–78.0)	67.0 (59.0–78.0)
Education			
College	991	37.8	37.7
High school	991	28.7	28.5
Less than high school	991	33.5	33.8
Marital status			
Never married	994	7.3	7.3
Married or living with someone		47.7	47.6
Widowed		23.6	23.6
Divorced/separated		21.3	21.3
Prestroke characteristics			
IQCode, range = 1–5			
≤3	876	49.2	49.6
>3–4		43.4	43.0
>4		7.42	7.4
mRS, range = 0–5			
0–1	978	42.3	42.0
2–3		45.8	45.9
≥4		11.9	12.1
Current smoker	992	22.1	22.1
Alcohol intake per week			
Does not drink	995	22.6	22.6
<1 drink		46.5	46.5
1–14 drinks		24.9	24.9
15 or more drinks		5.9	5.9
Stroke characteristics			
NIHSS	991	3.0 (1.0–7.0)	3.0 (1.0–7.0)
Treatment with tPA	995	14.3	14.3
Vascular risk factors			
Body mass index	995	28.3 (24.9–32.8)	28.3 (24.9–32.8)
Atrial fibrillation	993	13.6	13.6
Coronary artery disease	993	29.6	29.6
Diabetes	995	47.4	47.4
Hypertension	995	80.7	80.7
High cholesterol	994	51.6	51.6
History of stroke/TIA	994	28.1	28.0

IQCode = Informant Questionnaire on Cognitive Decline in the Elderly; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack; tPA = tissue plasminogen activator.

TABLE 2. Sleep and Outcome Characteristics for Complete and Imputed Data

Variable	n	Complete Data Median (IQR)	Imputed Data, n = 995, Median (IQR)
Sleep measures			
REI	623	14.0 (6.0–25.0)	13.0 (6.0–26.0)
SDB, REI $\geq$ 10	623	62.8	62.7
90-day stroke outcomes			
ADL/IADL score, range = 1–4	974	2.2 (1.4–3.3)	2.2 (1.4–3.3)
NIHSS, range 1–42	948	2.0 (0.0–5.0)	2.0 (0.0–5.0)
3MSE	770	88.0 (78.0–94.0)	87.0 (73.0–94.0)
SS-QOL	990	3.3 (2.3–4.3)	3.3 (2.3–4.3)

3MSE = modified Mini-Mental State Examination; ADL = activities of daily living; IADL = instrumental activities of daily living; IQR = interquartile range; NIHSS = National Institutes of Health Stroke Scale; REI = respiratory event index; SDB = sleep-disordered breathing; SS-QOL = Stroke Specific Quality of Life.

14 (IQR = 6–25), and 62.8% had SDB (REI  $\geq$ 10). Median central apnea index was 0 (IQR = 0–2). Participants, on average, had favorable 90-day outcomes. Median ADL/IADL score (range = 1–4, higher scores are worse) was 2.2 (IQR = 1.4–3.3), median NIHSS was 2.0 (IQR = 0–5.0), median 3MSE score was 88 (IQR = 78–94), and median SS-QOL (range = 1–5, higher scores are worse) was 3.3 (IQR = 2.3–4.3).

### SDB and 90-Day Stroke Outcomes

SDB was significantly associated with worse functional and cognitive outcomes after adjustment for confounders (Table 3). Subjects with SDB scored on average 0.15 points higher on the ADL/IADL score ( $\beta$  = 0.15, 95% confidence interval [CI] = 0.01–0.28) and 2.66 points lower on the 3MSE than those without SDB ( $\beta$  = –2.66, 95% CI = –4.85 to –0.47). SDB was not associated with neurologic or QOL outcomes at 90 days.

### Ethnicity, SDB, and 90-Day Stroke Outcomes

Prevalence of SDB was 69.2% in MAs and 53.5% NHWs. MA ethnicity was adversely associated with all 4 stroke outcomes after adjustment (Table 4). After including SDB in the models, the ethnicity association was attenuated by –9% for functional outcome, 10% for cognitive outcome, 6% for QOL, and 4% for neurologic outcome. Formal tests for effect modification of the SDB–stroke outcome associations by ethnicity suggested possible ethnic differences for cognitive outcome and QOL ( $p$  for interaction  $\leq$ 0.15; Table 5). For cognitive outcome, the association with SDB was stronger and reached statistical significance for MAs ( $\beta$  = –3.97, 95% CI = –6.63 to –1.31) as opposed to NHWs, among whom no association was observed ( $\beta$  = –0.40, 95% CI = –4.18 to 3.39). PAR% for SDB and cognitive outcomes suggest that, if SDB is causally related to cognitive outcome, –8% of poor poststroke cognitive outcomes in MAs could be eliminated if

TABLE 3. Adjusted<sup>a</sup> Associations between Sleep-Disordered Breathing and 90-Day Stroke Outcomes

	ADL/IADL, Range = 1–4, Mean Difference (95% CI)	3MSE, Range = 0–100, Mean Difference (95% CI)	NIHSS, Range = 1–42, Relative Difference <sup>a</sup> (95% CI)	SS-QOL, Range = 1–5, Mean Difference (95% CI)
SDB, REI $\geq$ 10, yes vs no	0.15 (0.01–0.28)	–2.66 (–4.85 to –0.47)	1.11 (0.94–1.31)	–0.09 (–0.23 to 0.06)

<sup>a</sup>Models are adjusted for sociodemographics (age, sex, ethnicity, education, marital status), prestroke functional disability (modified Rankin Scale) and cognitive impairment (Informant Questionnaire on Cognitive Decline in the Elderly), health-risk behaviors (alcohol intake, smoking), initial NIHSS, treatment with tissue plasminogen activator, and vascular risk factors (body mass index, atrial fibrillation, coronary artery disease, diabetes, hypertension, high cholesterol, history of stroke/transient ischemic attack).

3MSE = modified Mini-Mental State Examination; ADL = activities of daily living; CI = confidence interval; IADL = instrumental activities of daily living; NIHSS = National Institutes of Health Stroke Scale; REI = respiratory event index; SDB = sleep-disordered breathing; SS-QOL = Stroke Specific Quality of Life.

**TABLE 4. Adjusted<sup>a</sup> Associations Between Ethnicity and Ninety-day Stroke Outcomes Before and After Adjustment for Sleep-Disordered Breathing**

Model	ADL/IADL, Range = 1–4, Mean Difference (95% CI)	3MSE, Range = 0–100, Mean Difference (95% CI)	NIHSS, Range = 1–42, Mean Difference (95% CI)	SS-QOL, Range = 1–5, Mean Difference (95% CI)
Ethnicity, MA vs NHW, without SDB in model	0.20 (0.09–0.31)	–3.22 (–5.50 to –0.94)	1.34 (1.16–1.55)	–0.17 (–0.31 to –0.03)
Ethnicity, MA vs NHW, with SDB in model	0.18 (0.07–0.30)	–2.90 (–5.16 to –0.64)	1.32 (1.14–1.53)	–0.16 (–0.30 to –0.02)
Change in ethnicity association comparing models without and with SDB	8.6%	9.9%	4.3%	6.0%

<sup>a</sup>Models are adjusted for sociodemographics (age, sex, ethnicity, education, marital status), prestroke functional disability (modified Rankin Scale) and cognitive impairment (Informant Questionnaire on Cognitive Decline in the Elderly), health-risk behaviors (alcohol intake, smoking), initial NIHSS, treatment with tissue plasminogen activator, and vascular risk factors (body mass index, atrial fibrillation, coronary artery disease, diabetes, hypertension, high cholesterol, history of stroke/transient ischemic attack).  
3MSE = modified Mini-Mental State Examination; ADL = activities of daily living; CI = confidence interval; IADL = instrumental activities of daily living; MA = Mexican American; NHW = non-Hispanic white; NIHSS = National Institutes of Health Stroke Scale; SDB = sleep-disordered breathing; SS-QOL = Stroke Specific Quality of Life.

SDB were eliminated. For QOL, SDB showed no association in MAs ( $\beta = -0.17$ , 95% CI =  $-0.38$  to  $0.03$ ) or NHWs ( $\beta = 0.11$ , 95% CI =  $-0.14$  to  $0.36$ ).

**Discussion**

Results from this large and diverse population-based sample of ischemic stroke patients show that significant SDB shortly after the event is associated with worse functional and cognitive function at 90 days poststroke. This association persisted

despite comprehensive adjustment for confounding factors, and for potential selection bias. These results raise the hypothesis that SDB treatment may improve stroke recovery in these critical outcome domains. If SDB treatment is proven to be effective, this therapy could have a substantial impact on the growing number of disabled stroke survivors, as the majority have SDB.<sup>4</sup>

Pilot RCTs have evaluated the effect of CPAP on functional and cognitive outcomes, with mixed results.<sup>6,16,18,20–24</sup>

**TABLE 5. Adjusted<sup>a</sup> Ethnic-Specific Associations between Sleep-Disordered Breathing and 90-Day Stroke Outcomes**

	ADL/IADL, Range = 1–4, Mean Difference (95% CI)	3MSE, Range = 0–100, Mean Difference (95% CI)	NIHSS, Range = 1–42, Mean Difference (95% CI)	SS-QOL, Range = 1–5, Mean Difference (95% CI)
NHW	0.10 (–0.10 to 0.29)	–0.40 (–4.18 to 3.39)	0.99 (0.78–1.25)	0.11 (–0.14 to 0.36)
MA	0.16 (–0.03 to 0.35)	–3.97 (–6.63 to –1.31)	1.16 (0.92–1.47)	–0.17 (–0.38 to 0.03)
Ethnicity × SDB interaction, <i>p</i>	0.65	0.15	0.33	0.11

<sup>a</sup>Models are adjusted for sociodemographics (age, sex, ethnicity, education, marital status), prestroke functional disability (modified Rankin Scale) and cognitive impairment (Informant Questionnaire on Cognitive Decline in the Elderly), health-risk behaviors (alcohol intake, smoking), initial NIHSS, treatment with tissue plasminogen activator, and vascular risk factors (body mass index, atrial fibrillation, coronary artery disease, diabetes, hypertension, high cholesterol, history of stroke/transient ischemic attack), as well as the interactions between ethnicity and these covariates.  
3MSE = modified Mini-Mental State Examination; ADL = activities of daily living; CI = confidence interval; IADL = instrumental activities of daily living; MA = Mexican American; NHW = non-Hispanic white; NIHSS = National Institutes of Health Stroke Scale; SDB = sleep-disordered breathing; SS-QOL = Stroke Specific Quality of Life.

The majority of trials were conducted in stroke rehabilitation units or a limited number of hospitals, with sample sizes ranging from 30 to 252. Our results now suggest that functional and cognitive outcomes are reasonable targets for larger, adequately powered trials of the effectiveness of CPAP in improving stroke outcomes. Functional and cognitive outcomes as opposed to QOL and NIHSS appear more likely to show benefit. An ongoing, multicenter phase 3 clinical trial (Sleep for Stroke Management and Recovery Trial, or Sleep SMART) will test whether treatment of SDB with CPAP after an ischemic stroke or TIA improves 90-day outcomes. With functional status as the primary outcome, and cognition as a secondary endpoint, Sleep SMART could provide definitive evidence as to the potential for SDB treatment to improve stroke outcomes.

Our results suggest that SDB contributes to worse outcomes in MAs compared with NHWs via 2 pathways. First, as described above, we demonstrated that SDB was associated with worse functional and cognitive outcomes. As SDB is also more prevalent in MAs,<sup>4</sup> SDB appears to help explain the association between ethnicity and functional and cognitive outcomes. Our results suggest that 9 to 10% of the ethnic disparity in these outcomes is explained by SDB. Second, our results suggested a stronger association between SDB and worse cognitive outcome in MAs than in NHWs. We approximated that 8% of poor cognitive outcomes could be eliminated in the MA stroke population if SDB were eliminated, a conservative estimate given the definition used to define poor outcome. Therefore, effective treatment for SDB holds some promise for reducing poor functional and cognitive outcomes in the growing number of MA stroke survivors, although our estimates suggest that additional interventions will also be needed to reduce outcome disparities.

The suggested stronger association between SDB and cognitive outcome in MAs compared with NHWs raises the question of potential mechanisms. The finding is not driven by ethnic differences in severity of SDB or in treatment of SDB poststroke based on our previous work.<sup>4,40</sup> Alternatively, downstream consequences of SDB may vary by ethnicity. For example, MAs may experience lower blood oxygen levels during sleep, greater reductions in sleep efficiency, greater reductions in slow wave or rapid eye movement sleep, or greater reduction in spindle activity, which may translate into poorer cognitive outcome.<sup>41–44</sup> Another possibility is synergistic effects of SDB and other risk factors for poor stroke outcome. For example, individuals with diabetes and low sleep efficiency have poorer cognitive function than those with higher sleep efficiency.<sup>45</sup> Synergistic effects between SDB and obesity on cognitive function have also been observed.<sup>46</sup> MAs with stroke have higher prevalence of both diabetes and obesity than NHWs.<sup>26</sup> More research is

needed to understand mechanisms linking SDB to cognitive outcomes in MAs. Use of full polysomnography—even if unattended, to make it a feasible option just after stroke—might allow greater characterization of poststroke SDB. Such research would speak to the potential for existing SDB treatments to improve cognitive outcome in MAs with stroke, or possibly indicate whether novel treatment targets are needed. Our finding of ethnic differences in the SDB–cognitive outcome association also suggests the need for future studies, and perhaps clinical trials, to evaluate relationships within groups defined by race–ethnicity.

This study is the first large, population-based study of SDB and QOL in stroke patients. Use of patient-reported outcomes, such as QOL, in stroke research is growing with the recognition that measuring patient-perceived health status is critical to improvement of patient outcomes and involvement of patients more directly in stroke care decisions.<sup>47</sup> Although we found no overall association between SDB just after stroke and QOL at 90 days, an association was suggested in MAs, consistent with the observed adverse effects of SDB on the other stroke outcomes in this ethnic group. Literature on the association of SDB and QOL in stroke patients is limited. One small study of 22 stroke patients showed a correlation between impaired sleep quality and QOL, which is consistent with our findings.<sup>48</sup> Outside of stroke, SDB is associated with poorer QOL, and treatment of moderate to severe SDB with CPAP improves QOL.<sup>49,50</sup> Additional research is needed to understand the impact of SDB on a broader range of patient-reported outcomes critical to healthy living, such as sexual function, work, and social engagement, among others.

There are limitations that warrant discussion. Given the logistical challenges with full polysomnography in stroke patients, we used an HSAT. The device used has been well validated when using the 4% desaturation criterion to define hypopneas, suggesting minimal misclassification of SDB. Our statistical methods included use of imputation and IPWs to minimize selection bias, a strength of the study. However, there was a considerable degree of missing data and there may be patients who were eligible for the study but not represented in the sample and therefore cannot be accounted for by IPW methods. For these reasons, some caution in the interpretation of our results is advised. Although our sample size was large, the study may have been underpowered to detect effect modification. Furthermore, although our consideration of effect modification of the SDB–outcome associations by ethnicity was justified based on our a priori hypothesis of potential differences in pathophysiology of SDB by ethnicity, our results regarding the presence of effect modification should be interpreted with caution and require replication in other studies. Given that our intent was to assess causal associations, we adjusted for



all possible confounders. It is possible that some factors, such as hypertension and diabetes, are on the causal pathway, and therefore we may have overadjusted. However, our previous work suggests that these factors are not associated with functional and cognitive outcomes, arguing against the mediation hypothesis.<sup>26</sup> Finally, we a priori hypothesized that SDB confounds the association between ethnicity and stroke outcomes. It is also possible that SDB serves as a mediator of the ethnicity–stroke outcome associations, and this warrants further investigation.

### Summary

Significant SDB just after stroke shows associations with worse functional and cognitive outcomes at 90 days. The potential for an underlying causal effect raises the possibility that identification and treatment of SDB after stroke could have substantial impact on recovery. Functional and cognitive outcomes appear to be reasonable endpoints for RCTs of SDB treatments in stroke patients. Moreover, SDB may contribute to these outcomes disproportionately in MAs compared with NHWs, suggesting that effective poststroke SDB treatment may lessen ethnic stroke disparities.

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### Author Contributions

L.D.L., R.D.C., L.B.M., and D.L.B. contributed to the conception and design of study; L.D.L., B.N.S., D.L., E.C., S.T., and D.L.B. contributed to the acquisition and analysis of data; L.D.L., B.N.S., D.L., R.D.C., and D.L.B. drafted a significant portion of the manuscript.

### Potential Conflicts of Interest

Nothing to report.

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