

Sleep Parameters of Breathing and Cognitive Function in a Diverse Hispanic/Latino Cohort

Kevin A. González, MS; Wassim Tarraf, PhD; Shanmin Sultana, BS; Barbara Junco, MS; Eena Kosik, BS; Bradley Voytek, PhD; Hector M. González, PhD; and Alberto R. Ramos, MD, MSPH, FAASM

BACKGROUND: Sleep-disordered breathing (SDB) is common and associated with worse cardiovascular and brain health. Hispanic/Latino individuals are at increased risk for SDB. OSA is the most studied SDB; it is characterized by apnea-hypopnea events and has been linked to adverse vascular health and cognitive sequelae. Less is known about upstream factors such as parameters of breathing. Breathing dynamics such as breathing rate and breathing rate variability have been linked to changes in mood and oscillatory brain activity. Their relationships with cognitive performance, particularly in diverse and understudied Hispanic/Latino communities, are unknown.

RESEARCH QUESTION: What is the association between parameters of breathing and cognitive outcomes?

STUDY DESIGN AND METHODS: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a prospective study of diverse Hispanic/Latino participants. Individuals were given a home sleep apnea device for in-home sleep testing. Breathing information was extracted from the cannula channel, and parameters of breathing were calculated by using bycycle, a novel tool for time series analysis. A total of 6,737 individuals were included in the study.

RESULTS: Faster breathing rate was linked with worse domain-specific and global cognitive performance ($\beta_{\text{global}} = -0.011$; $P < .01$), and breathing rate variability was associated with worse global cognitive performance ($\beta_{\text{global}} = -0.022$; $P < .05$). In interaction models, breathing rate variability was found to be significantly associated with worse verbal fluency and global cognitive performance in women but not in men.

INTERPRETATION: Parameters of breathing are novel methods for understanding SDB and cognitive function. These results also suggest that faster breathing rate variability in women, but not in men, is related to worse cognitive function. CHEST Pulmonary 2025; 3(1):100102

KEY WORDS: cognition; sleep; sleep-disordered breathing; Latino subjects

ABBREVIATIONS: B-SEVLT = Brief Spanish-English Verbal Learning Test; BR = breathing rate; BRV = breathing rate variability; DSS = Digit Symbol Substitution; REI = respiratory event index; SDB = sleep-disordered breathing; WF = word fluency

AFFILIATIONS: From the Department of Neurosciences (K. A. G. and H. M. G.), University of California San Diego School of Medicine, San Diego, CA; Department of Healthcare Sciences and Institute of Gerontology (W. T. and S. S.), Wayne State University, Detroit, MI; Department of Neurology (B. J. and A. R. R.), University of Miami Miller School of Medicine, Miami, FL; and the Department of Cognitive Science (E. K. and B. V.) and Halıcıoğlu Data Science Institute (B. V.), Neurosciences Graduate Program, Kavli Institute for Brain and Mind, University of California, San Diego, La Jolla, CA.

Part of this article has been presented at the Alzheimer's Association International Conference 2023, July 16-20, 2023, Amsterdam, the Netherlands.

CORRESPONDENCE TO: Alberto Ramos, MD, MSPH, FAASM; email: a.amos1@med.miami.edu

Copyright © 2024 The Authors. Published by Elsevier Inc under license from the American College of Chest Physicians. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

DOI: <https://doi.org/10.1016/j.chpulm.2024.100102>

Take-home Points

Study Question: Our goal was to examine whether sleep breathing patterns were correlated with cognitive performance in a population of diverse Hispanic/Latino communities.

Results: We found that faster breathing was associated with worse domain-specific and global cognitive performance, whereas higher breathing rate variability was only associated with worse global cognitive performance.

Interpretation: Sleep breathing patterns could provide novel insights into cognitive health; future work should examine pathophysiologic mechanisms.

An estimated 50 to 70 million US adults have a sleep disorder.¹ Sleep disorders are more prevalent among older adults^{2,3} and possibly among Hispanic/Latino individuals compared with non-Hispanic White individuals.⁴ Sleep disorders have been linked to poor health outcomes, including type 2 diabetes, cardiovascular disease, depression, and higher mortality.^{5,6} Sleep disorders account for an estimated \$94.9 billion in incremental health care costs in the United States.⁷ Sleep is a prime modifiable risk factor for clinical and pharmacologic interventions over the life course; identifying sleep symptoms and their sequelae in cognitive aging and cognitive disorders is therefore a priority for the National Institutes of Health and the National Institute on Aging.

Sleep disorders may adversely affect cognitive health. A systematic review provided consistent evidence that sleep-disordered breathing (SDB) increases the risk for cognitive impairment in middle-aged adults.⁸ Several studies have found that self-reported sleep apnea accelerates cognitive decline and the onset of cognitive impairment.⁹⁻¹² Most of these studies focused predominantly on non-Hispanic White samples, and little to no research has examined upstream factors such as sleep parameters of breathing. Disordered breathing

could be indicative of changes in autonomic function.¹³ Indeed, Miglis et al¹³ suggested that intermittent hypoxia and sleep fragmentation could lead to sympathetic activation, with downstream sequelae in cardiovascular outcomes.¹⁴ Because cardiovascular disease has been linked to increased odds of dementia,¹⁵ sympathetic activation could mediate the effects of SDB on cognitive outcomes. Although breathing dynamics have been linked to changes in cognition, mood, and oscillatory brain activity,¹⁶⁻¹⁸ little research exists linking parameters of breathing during sleep (eg, breathing rate [BR] or breathing rate variability [BRV]) to cognitive outcomes.

Sex and age are important factors in understanding relationships between sleep and cognition. Hispanic/Latino individuals are understudied in sleep research despite increased risk for insomnia-like sleep disorders, including fragmented sleep and poorer sleep quality.¹⁹ Aging also has distinct effects on sleep and cognition, yet studies on how aging affects particular sleep disorders and their effects on cognitive functioning remain understudied.³ Metabolic syndrome,²⁰ greater exposure to stress,²¹ poor sleep quality,²² and OSA status¹² amplify the impact of older age on sleep-related cognitive impairment. The role of age in sleep dysfunction and cognition warrants further research, particularly in diverse Hispanic/Latino communities.

Traditional methods to ascertain parameters of breathing are onerous and inaccessible for large-scale studies. The current study used a novel tool to quantify parameters of breathing in a large and diverse Hispanic/Latino sample. Two features, BR and BRV, were derived and their relationships with function examined among diverse Hispanic/Latino individuals. We hypothesized that faster BR and increased BRV would be associated with lower cognitive function. Given that SDB is rarely studied outside of sleep apnea events, this novel approach may elucidate mechanisms by which breathing may be linked to cognitive disorders and other important health outcomes.

Study Design and Methods

Population

This study used data from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL; 2008-2011), which is a multisite, prospective cohort study of diverse Hispanic/Latino participants. A total of 16,415 diverse Hispanic/Latino (18-74 years old) individuals

were sampled from four major metropolitan cities: Bronx, New York; Miami, Florida; Chicago, Illinois; and San Diego, California. The goals of HCHS/SOL are to examine cardiovascular disease risk factors among a diverse Hispanic/Latino cohort. The HCHS/SOL parent study (N = 12,088) obtained both sleep questionnaires and in-home sleep testing data to ascertain and

TABLE 1] Descriptive Statistics Grouped According to Sex

Characteristic	Female	Male	Total	P Value
Unweighted N	4,206	2,551	6,757	...
%	55.3	44.7	100.0	...
Age, y	56.66 ± 10.60	56.03 ± 8.87	56.38 ± 9.85	.035
BMI, kg/m ²	30.47 ± 7.40	28.99 ± 5.15	29.81 ± 6.46	< .001
REI 3%	6.39 ± 12.54	10.50 ± 15.42	8.23 ± 14.46	< .001
Breathing rate	16.15 ± 3.58	16.18 ± 3.25	16.16 ± 3.45	.801
Breathing rate variability	-0.12 ± 0.98	0.13 ± 0.94	-0.01 ± 0.98	< .001
Hispanic/Latino background				
Dominican	10.47 (0.83)	8.49 (0.95)	9.59 (0.76)	.002
Central American	7.36 (0.55)	5.56 (0.53)	6.56 (0.45)	...
Cuban	23.72 (1.95)	29.92 (2.50)	26.49 (2.07)	...
Mexican	32.03 (1.94)	30.73 (2.01)	31.45 (1.79)	...
Puerto Rican	18.00 (1.25)	17.64 (1.22)	17.84 (1.07)	...
South American	5.98 (0.49)	5.06 (0.50)	5.57 (0.38)	...
Other/mixed	2.43 (0.60)	2.59 (0.39)	2.51 (0.39)	...
Education				
Less than high school	40.78 (1.31)	37.04 (1.45)	39.11 (1.06)	.037
High school or equivalent	20.00 (1.16)	23.42 (1.07)	21.53 (0.86)	...
More than high school	39.22 (1.35)	39.53 (1.51)	39.36 (1.07)	...
Field center				
Bronx, NY	28.23 (1.94)	24.33 (1.70)	26.49 (1.70)	.022
Chicago, IL	12.03 (0.86)	13.92 (1.13)	12.87 (0.90)	...
Miami, FL	34.95 (2.39)	37.23 (2.73)	35.97 (2.41)	...
San Diego, CA	24.79 (1.88)	24.52 (1.99)	24.67 (1.77)	...
Currently smokes	15.94 (0.91)	24.67 (1.29)	19.84 (0.86)	< .001
Alcohol use	35.57 (1.27)	58.31 (1.44)	45.72 (0.97)	< .001
Asthma	20.51 (1.16)	11.62 (0.80)	16.54 (0.78)	< .001

Data are presented as mean ± SD or % (SE) unless otherwise indicated. REI = respiratory event index.

quantify sleep patterns. At all testing centers, institutional review board approval was obtained for the study. Individuals provided written informed consent in their preferred language in accordance with the Declaration of Helsinki.

Study Details

A total of 8,303 individuals were aged ≥ 45 years and had cognitive testing data available, including 8,163 with sleep questionnaire data. A total of 7,377 participants had information on respiratory measures. After processing raw cannula recordings and excluding those with low-quality data or not enough data, a total of 6,886 with breathing information were extracted. We excluded observations with missing covariables. The final analytic sample was 6,757.

Individuals were administered sleep questionnaires and cognitive assessments in the individual's preferred language (Spanish or English). They underwent a single-night, at-home sleep apnea test using the Apnea Risk Evaluation System (ARES Unicorder 5.2; B-Alert).²³ The ARES Unicorder is a validated system that records multiple signals collected during home sleep apnea testing, including airflow in and out of the nostrils measured by a nasal pressure transducer, through a nasal cannula with a sampling rate of 10 Hz. Raw data from the cannula channel were used to derive BR and BRV.

Breathing signals were processed using the bicycle python package developed by Cole and Voytek.²⁴ In short, bicycle uses time-based, instead of traditional frequency-based, methods to analyze time series data. Bicycle detects peaks, troughs, and midpoints in

TABLE 2] Associations Between Breathing Parameters and Cognitive Outcomes

Parameter	B-SEVLT Summary		B-SEVLT Recall	
	Model 1	Model 2	Model 1	Model 2
	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)
Breathing rate	-0.010 ^a (-0.019 to -0.001)	-0.009 ^a (-0.018 to -0.001)	-0.009 (-0.019 to 0.001)	-0.008 (-0.018 to 0.002)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Breathing rate variability	-0.023 (-0.053 to 0.007)	-0.020 (-0.051 to 0.010)	-0.023 (-0.055 to 0.008)	-0.018 (-0.050 to 0.013)
	World Fluency		Digit Symbol Substitution	
	Model 1	Model 2	Model 1	Model 2
	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)
Breathing rate	-0.019 ^b (-0.032 to -0.006)	-0.014 ^a (-0.027 to -0.001)	-0.017 ^c (-0.026 to -0.008)	-0.016 ^c (-0.024 to -0.007)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Breathing rate variability	-0.052 ^a (-0.095 to -0.010)	-0.039 (-0.080 to 0.002)	-0.017 (-0.051 to 0.017)	-0.010 (-0.043 to 0.022)
	Global Cognition			
	Model 1	Model 2		
	b (95% CI)	b (95% CI)		
Breathing rate	-0.013 ^c (-0.020 to -0.006)	-0.011 ^b (-0.019 to -0.004)		
	β (95% CI)	β (95% CI)		
Breathing rate variability	-0.029 ^a (-0.052 to -0.006)	-0.022 ^a (-0.044 to -0.000)		

β = standardized regression coefficient; b = unstandardized regression coefficient; B-SEVLT= Brief Spanish-English Verbal Learning Test. Model 1 includes for continuous age, dichotomous sex (male, female), Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), and education (less than high school, high school or equivalent, more than high school). Model 2 additionally includes for cigarette use (does not smoke, currently smokes), alcohol use (does not drink, drinks; based on > 1 drink per day), continuous BMI, continuous respiratory event index (3%), testing center (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California), and asthma (no asthma, asthma).

^a $p < .05$.

^b $p < .01$.

^c $p < .001$.

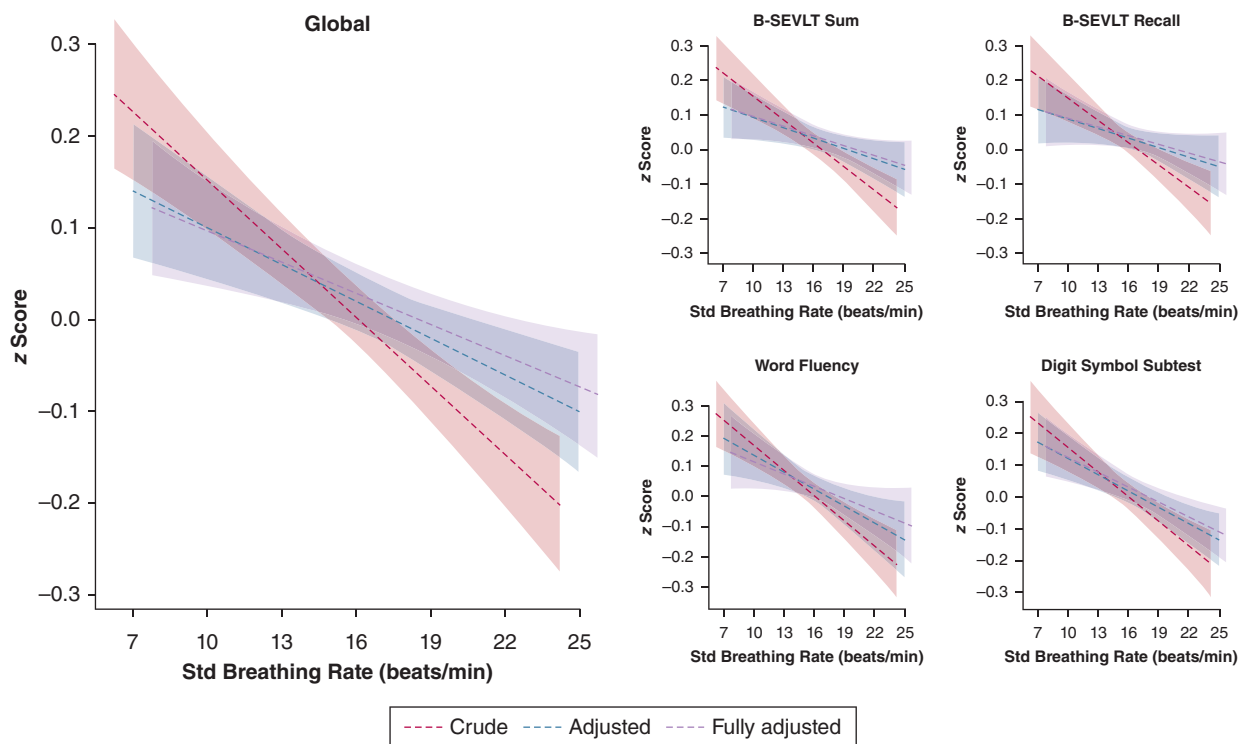


Figure 1 – Associations between breathing rate and cognitive function. The models were defined as follows. Model 0: unadjusted. Model 1: model includes for continuous age, dichotomous sex (male, female), Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), and education (less than high school, high school or equivalent, more than high school). Model 2: additionally includes for cigarette use (does not smoke, smokes), alcohol use (does not drink, drinks; based on > 1 drink per day), continuous BMI, continuous respiratory event index (3%), testing center (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California), and asthma (no asthma, asthma). B-SEVLT Sum = Brief Spanish-English Verbal Learning Test summary; Std = standardized.

breathing cycles to extract 10 parameters that describe the waveform of each breath, such as the rise and decay durations, amplitudes, and symmetry. This approach is adopted from the Matlab BreathMetrics toolbox, which has been validated in human data.²⁵ Although extraction of breathing parameters is automated, bicycle requires user input on four different heuristics to optimize identification of breathing cycles. Further information on methodology is provided in [e-Appendix 1](#). Individuals with < 250 total breathing cycles (ie, inhales and exhales) were not further processed. This was done to ensure that every individual had enough data to create robust measures (< 3% of individuals with breathing cycle data had < 250 cycles). We extracted several measures based on breathing detection and calculated the average BR and BRV for the whole recording.

Cognitive testing was administered during onsite interviews to middle-aged and older Hispanic/Latino subjects. Bilingual technicians were trained and supervised by the Cognitive Reading Center to ensure generalizability across the four sites. Technicians administered the following tests: (1) Brief Spanish-English Verbal

Learning Test (B-SEVLT), summary and delayed recall, which assesses learning and memory^{26,27}; (2) word fluency (WF) test from the Multilingual Aphasia Examination, which measures verbal fluency²⁸; and the (3) Digit Symbol Substitution (DSS) test, which assesses cognitive processing speed.²⁹ Each of these measures was standardized (*z* scored) to aid in interpretability across tests. Global performance was assessed by averaging the four normalized cognitive measures. Further information on cognitive testing and methodology has been detailed in a previous publication.³⁰

Outcomes include standardized B-SEVLT Summary, B-SEVLT Recall, WF, DSS, and global performance. Exposures include BR (breaths per minute) and BRV (interquartile range of BR; log-transformed and standardized). Covariates include continuous age, dichotomous sex (male, female), Hispanic/Latino heritage (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), education (less than high school, high school or equivalent, more than high school), smoking status (never or formerly smoked, currently smokes), alcohol use (never drinks, drinks;

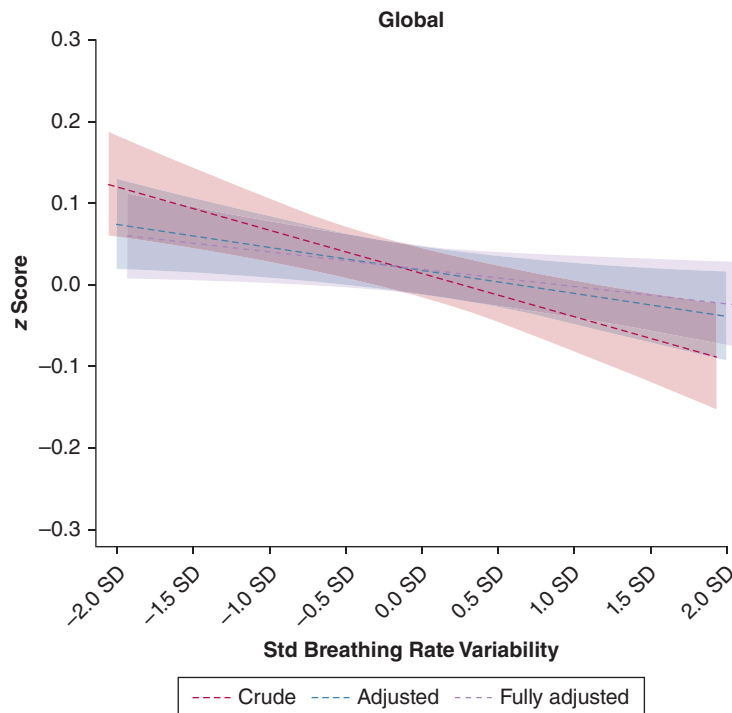


Figure 2 – Associations between breathing rate variability and global cognitive function. The models were defined as follows. Model 0: unadjusted. Model 1: model includes for continuous age, dichotomous sex (male, female), Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), and education (less than high school, high school or equivalent, more than high school). Model 2: additionally includes for cigarette use (does not smoke, currently smokes), alcohol use (does not drink, drinks; based on > 1 drink per day), continuous BMI, continuous respiratory event index (3%), testing center (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California), and asthma (no asthma, asthma). Breathing rate variability was log-transformed due to its non-normal distribution and z scored to aid in interpretability. SD changes in the z score provide information of cognitive performance by percentile in breathing variability relative to the target population. Std = standardized.

based on > 1 drink per day), continuous BMI, continuous respiratory event index (REI; 3% desaturation), testing center (Bronx, Chicago, Miami, and San Diego), and asthma (no asthma, asthma; self-report).

Data Analysis

Subsequent data analysis on processed breathing signals was performed by using Stata 17 (StataCorp). First, we generated descriptive statistics over our exposures and covariates of interest based on sex groupings. Differences across sex groupings were tested by using F tests and χ^2 tests for continuous and categorical indicators, respectively (Table 1). Next, survey-weighted linear regression models were run on each of the outcomes

using several modes: (1) crude; (2) age, sex, education, background; and (3) full covariate adjusted models.

Beta (β when both exposure and outcomes are standardized; b when only the outcome is standardized) estimates and 95% CIs are presented in Table 2. To aid in interpretation of findings, marginal estimates were plotted for both exposures (Figs 1, 2). Next, we assessed sex modifications on our exposures. The significance of the models was estimated by using an F test, and results are presented in Table 3. Stratified sex models were run on significant models, and these data are presented in Table 4 and Figure 3. In supplemental models, we assessed age modifications on our exposures of interest. Results from these models are presented in e-Tables 1 and 2 and e-Figure 1.

Results

Descriptive statistics are presented in Table 1. Female participants comprised 55.3% of individuals in this study. The average BR for the sample was 16.16 ± 3.45 breaths/min, and no sex differences were found based on the χ^2 test. On average, female participants, compared

with male participants, were older; they had lower REI, BRV, smoking prevalence, and alcohol use but higher asthma rates and BMI. A total of 4,012 (approximately 59%) had an REI < 5; 1,739 (approximately 25%) had an REI of 5 to 15; and 1,006 (approximately 15%) had an REI ≥ 15 .

TABLE 3] Test of Modification of Breathing Measures According to Sex Groupings

Model	B-SEVLT Summary			B-SEVLT Recall			Word Fluency			Digit Symbol Substitution			Global Cognition		
	F Test	P Value	df	F Test	P Value	df	F Test	P Value	df	F Test	P Value	df	F Test	P Value	df
Breathing variability															
M0	4.04	.04	1.00	7.59	.01	1.00	4.51	.03	1.00	0.03	.87	1.00	4.83	.03	1.00
M1	3.58	.06	1.00	5.95	.01	1.00	4.46	.04	1.00	0.06	.81	1.00	6.19	.01	1.00
M2	2.90	.09	1.00	5.40	.02	1.00	3.73	.05	1.00	0.00	.96	1.00	5.02	.03	1.00
Breathing rate															
M0	0.34	.56	1.00	0.84	.36	1.00	1.04	.31	1.00	1.24	.27	1.00	0.11	.74	1.00
M1	0.82	.37	1.00	1.28	.26	1.00	1.62	.20	1.00	0.89	.34	1.00	1.00	.32	1.00
M2	0.59	.44	1.00	1.04	.31	1.00	1.12	.29	1.00	1.34	.25	1.00	0.53	.47	1.00

B-SEVLT = Brief Spanish-English Verbal Learning Test. Model 0 (M0): unadjusted. Model 1 (M1): includes for continuous age, dichotomous sex (male, female), Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), and education (less than high school, high school or equivalent, more than high school). Model 2 (M2): additionally includes for cigarette use (does not smoke, currently smokes), alcohol use (does not drink, drinks; based on > 1 drink per day), continuous BMI, continuous respiratory event index (3%), testing center (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California), and asthma (no asthma, asthma).

TABLE 4] Associations Between Breathing Rate Variability and Cognitive Function

Parameter	B-SEVLT-Recall		Word Fluency		Global Cognition	
	Female	Male	Female	Male	Female	Male
Breathing variability	-0.026 (-0.059 to 0.008)	0.021 (-0.007 to 0.049)	-0.058 ^a (-0.104 to -0.012)	0.004 (-0.029 to 0.038)	-0.027 ^a (-0.048 to -0.007)	0.010 (-0.013 to 0.033)

Data are presented as β (95% CI). Results are based on stratified sex analyses. Model includes for continuous age, dichotomous sex (male, female), Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), education (less than high school, high school or equivalent, more than high school), cigarette use (does not smoke, smokes), alcohol use (does not drink, drinks; based on > 1 drink per day), continuous BMI, continuous respiratory event index (3%), testing center (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California), and asthma (no asthma, asthma). β = standardized regression coefficient; B-SEVLT = Brief-Spanish English Verbal Learning Test.

^a $p < .05$.

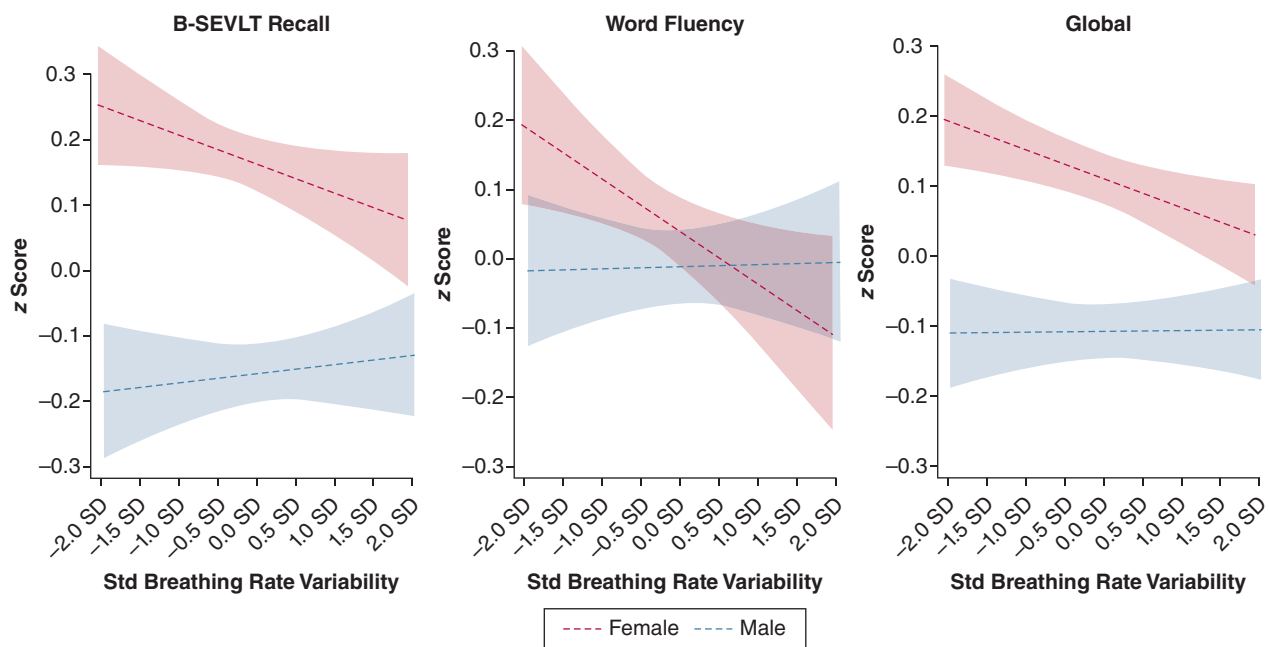


Figure 3 – Associations between breathing rate variability and cognitive function. Results are based on stratified sex analysis. The models were defined as follows. Model 0: unadjusted. Model 1: model includes for continuous age, dichotomous sex (male, female), Hispanic/Latino background (Central American, Cuban, Dominican, Mexican, Puerto Rican, South American), and education (less than high school, high school or equivalent, more than high school). Model 2: model additionally includes for cigarette use (does not smoke, smokes), alcohol use (does not drink, drinks; based on > 1 drink per day), continuous BMI, continuous respiratory event index (3%), testing center (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California), and asthma (no asthma, asthma). Breathing rate variability was log-transformed due to its non-normal distribution and z scored to aid in interpretability. SD changes in z score provide information of cognitive performance by percentile in breathing variability relative to the target population. Std = standardized. B-SEVLT = Brief Spanish-English Verbal Learning Test.

Faster breathing (BR) was negatively associated with learning ($b_{B-SEVLT-SUM} = -0.009$; 95% CI, -0.018 to -0.001 ; $P < 0.05$), verbal fluency ($b_{WF} = -0.014$; 95% CI, -0.027 to -0.001 ; $P < .05$), processing speed ($b_{DSS} = -0.016$; 95% CI, -0.024 to -0.007 ; $P < .001$), and global cognition ($b_{Global} = -0.011$; 95% CI, -0.019 to -0.004 ; $P < .01$). BRV was negatively associated with WF and global cognition ($\beta_{Global} = -0.022$; 95% CI, -0.044 to -0.000 ; $P < .05$), but only global cognition remained significant following full covariate adjustment (Figs 1, 2; Table 2).

Sex did not modify the associations between BR and cognition. For BRV, significant modifications were found in episodic memory, verbal fluency, and global cognition (Table 3). In stratified models, a negative association between BRV and cognition in female participants was noted for verbal fluency ($\beta_{WF} = -0.058$; 95% CI, -0.104 to -0.012 ; $P < .05$) and global cognition ($\beta_{Global} = -0.027$; 95% CI, -0.048 to -0.007 ; $P < 0.05$), but these associations were not present in male participants (Fig 3, Table 4).

In age modification models, significant modifications were found for BRV in verbal fluency and global cognition (e-Table 1). Stratified models show that those aged ≥ 65 years had strong negative associations

between BRV and cognitive function, although the CIs are large (e-Fig 1, e-Table 2).

Discussion

In the current analysis of large epidemiologic data on community-residing diverse Hispanic/Latino adults, a novel approach was used to relate parameters of breathing with cognitive performance. These findings suggest that BR and potentially BRV could be useful parameters of breathing to examine and potentially target for interventions in the context of cognitive health and aging.

We found that faster breathing was associated with worse cognitive performance. Faster breathing could be a biomarker for changes in parasympathetic/sympathetic balance. Gerritsen and Band³¹ proposed that slower breathing may lower the threshold for triggering a parasympathetic vagal response that reduces blood pressure and heart rate. Sympathetic changes could also play a role. OSA may be associated with sympathetic overactivity,³² and possible mechanisms include baroreceptor activation due to reduced oxygenation (ie, intermittent hypoxia) and arousal due to sleep fragmentation.¹³ Because changes in the

parasympathetic/sympathetic systems have been linked with cognitive change,³³ these breathing measures provide an opportunity to further elucidate these possible mechanisms in large epidemiologic studies.

We found that female participants had lower rates of BRV compared with male participants and that higher rates of BRV were associated with worse cognitive performance in female participants only. These results suggest possible baseline differences in parameters of breathing according to sex. Indeed, Pal et al³⁴ found that women had a lower BRV but the largest increase in BRV after performing a breath hold task. Sleep fragmentation is a suggested mechanism by which BRV leads to worse cognitive outcomes. For instance, in individuals without OSA, higher BRV is linked to increased wakefulness.³⁵ BRV therefore could be an indicator for fragmented sleep, which has been linked to sympathetic activation¹³ and decreased glymphatic clearance of aberrant proteins in brain (eg, amyloid beta).³⁶ Although the female participants in the current cohort have lower BRV compared with male participants, they are also at an increased risk for insomnia and sleep fragmentation.¹⁹ Most participants in this sample had low levels of OSA (based on REI), and thus these breathing markers could help create a more comprehensive picture of SDB and sleep health, as well as better characterize how these factors relate to cognition.

Significant modifications were also found in how BRs are related to cognition with older age, particularly for verbal fluency. Because the prevalence of SDB increases with age,³⁷ our results highlight the importance of sleep breathing problems and cognition for older individuals. A 2017 meta-analytic review found that sleep deprivation was linked to worse executive function, attention, and long-term memory,³⁸ all of which could be important for verbal fluency. Paradoxically, although the meta-analysis found that associations became stronger as individuals aged, these were not present in the oldest age group (≥ 60 years). Given the relatively young age of the current cohort (upper age range was 74 years), most individuals were cognitively healthy. As such, our findings can become more pronounced with aging of the cohort. Longitudinal analyses to examine cognitive change and potentially impairment outcomes are needed.

The current study had several strengths as well as limitations. HCHS/SOL is a cohort study of diverse

Hispanic/Latino communities; therefore, this work is critical in providing knowledge for such understudied populations. This study introduced novel standard parameters of sleep dysfunction and provides novel parameters that could be effective for clinical practice. Because of the large sample size, we were able to test for possible sex and age modifications, both known risk factors for cognitive aging. We have also accounted for several important confounders, such as REI, which allow us to better understand relationships between breathing and cognition regardless of OSA status. There are also some limitations to this work. First, we did not have sleep data on all individuals with cognitive testing, which may have affected our ability to detect associations between our novel sleep breathing parameters and cognitive function. Second, we only examined two of the 10 parameters extracted using the bicycle toolbox; more sleep breathing parameters could provide more comprehensive and nuanced assessments of dysfunctions in breathing. We also could not account for possible important confounders such as menopause or neuromuscular disorders that could affect these relationships. These possible confounders should be explored in future work. Lastly, this study includes individuals middle-aged up to 74 years, and thus it does not account for the full continuum of cognitive aging.

Interpretation

These novel sleep breathing parameters, outside of sleep apnea events, may be critical in understanding healthy cognitive aging, especially in older adults. Further research is needed to fully characterize breathing during sleep and how it correlates with cognitive function and aging.

Funding

A. R. R. and B. J. are funded by the Sleep in Neurocognitive Aging and Alzheimer's Research (SANAR) study (AG67568), and H. G., W. T., and K. A. G. are funded by SOL-INCA AD (AG075758). E. K. and S. S. are funded by their institutions. B. V. is funded through a combination of private and public funding (GM134363).

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Author contributions: K. A. G. generated the analysis, conceptualized the project, and wrote the manuscript. W. T. oversaw the statistical analysis and provided guidance throughout the project. A. R. R. provided important conceptual ideas regarding sleep health. E. K. and B. V. helped with data processing. S. S. assisted with writing the introduction and literature review. H. G. and B. J. provided writing feedback. All authors helped revise the manuscript.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Additional information: The e-Appendix, e-Figure, and e-Tables are available online under “Supplementary Data.”

References

1. National Heart and Lung, and Blood Institute. *What are sleep deprivation and deficiency? National Heart, Lung, and Blood Institute website.* <https://www.nhlbi.nih.gov/health/sleep-deprivation>
2. Gordon NP, Yao JH, Brickner LA, Lo JC. Prevalence of sleep-related problems and risks in a community-dwelling older adult population: a cross-sectional survey-based study. *BMC Public Health.* 2022;22(1):2045.
3. Dzierzewski JM, Dautovich N, Ravvits S. Sleep and cognition in older adults. *Sleep Med Clin.* 2018;13(1):93-106.
4. Roncoroni J, Okun M, Hudson A. Systematic review: sleep health in the US Latinx population. *Sleep.* 2022;45(7):zsc092.
5. Huyett P, Siegel N, Bhattacharyya N. Prevalence of sleep disorders and association with mortality: results from the NHANES 2009-2010. *Laryngoscope.* 2021;131(3):686-689.
6. Centers for Disease Control and Prevention. Sleep and chronic disease, Centers for Disease Control and Prevention website. https://www.cdc.gov/sleep/about_sleep/chronic_disease.html
7. Huyett P, Bhattacharyya N. Incremental health care utilization and expenditures for sleep disorders in the United States. *J Clin Sleep Med.* 2021;17(10):1981-1986.
8. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. *JAMA Neurol.* 2017;74(10):1237-1245.
9. Bratzke LC, Carlson BA, Moon C, Brown RL, Kosciak RL, Johnson SC. Multiple chronic conditions: Implications for cognition—findings from the Wisconsin Registry for Alzheimer’s Prevention (WRAP). *Appl Nurs Res.* 2018;42:56-61.
10. Walton SR, Brett BL, Chandran A, et al. Mild cognitive impairment and dementia reported by former professional football players over 50 yr of age: an NFL-LONG study. *Med Sci Sports Exerc.* 2022;54(3):424-431.
11. Shieu MM, Dunietz GL, Paulson HL, Chervin RD, Braley TJ. The association between obstructive sleep apnea risk and cognitive disorders: a population-based study. *J Clin Sleep Med.* 2022;18(4):1177-1185.
12. Ayalon L, Ancoli-Israel S, Drummond SP. Obstructive sleep apnea and age: a double insult to brain function? *Am J Respir Crit Care Med.* 2010;182(3):413-419.
13. Miglis MG. Autonomic dysfunction in primary sleep disorders. *Sleep Med.* 2016;19:40-49.
14. Grassi G, Seravalle G, Mancia G. Sympathetic activation in cardiovascular disease: evidence, clinical impact and therapeutic implications. *Eur J Clin Invest.* 2015;45(12):1367-1375.
15. Wolters FJ, Segufa RA, Darweesh SK, et al. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimer Dementia.* 2018;14(11):1493-1504.
16. Zelano C, Jiang H, Zhou G, et al. Nasal respiration entrains human limbic oscillations and modulates cognitive function. *J Neurosci.* 2016;36(49):12448-12467.
17. Nakamura NH, Oku Y, Fukunaga M. “Brain-breath” interactions: respiration-timing-dependent impact on functional brain networks and beyond. *Rev Neurosci.* 2023;35(2):165-182.
18. Maric V, Ramanathan D, Mishra J. Respiratory regulation & interactions with neuro-cognitive circuitry. *Neurosci Biobehav Rev.* 2020;112:95-106.
19. González KA, Tarraf W, Wallace DM, et al. Phenotypes of obstructive sleep apnea in the Hispanic Community Health Study/Study of Latinos. *Sleep.* 2021;44(12):zsab181.
20. Kaur SS, Tarraf W, Wu B, et al. Modifying pathways by age and sex for the association between combined sleep disordered breathing and long sleep duration with neurocognitive decline in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Alzheimer Dement.* 2021;17(12):1950-1965.
21. Deater-Deckard K, Chary M, McQuillan ME, Staples AD, Bates JE. Mothers’ sleep deficits and cognitive performance: moderation by stress and age. *PLoS One.* 2021;16(1):e0241188.
22. Byun E, Kim J, Riegel B. Associations of subjective sleep quality and daytime sleepiness with cognitive impairment in adults and elders with heart failure. *Behav Sleep Med.* 2017;15(4):302-317.
23. Westbrook PR, Levendowski DJ, Cvetinovic M, et al. Description and validation of the apnea risk evaluation system: a novel method to diagnose sleep apnea-hypopnea in the home. *Chest.* 2005;128(4):2166-2175.
24. Cole S, Voytek B. Cycle-by-cycle analysis of neural oscillations. *J Neurophysiol.* 2019;122(2):849-861.
25. Noto T, Zhou G, Schuele S, Templer J, Zelano C. Automated analysis of breathing waveforms using BreathMetrics: a respiratory signal processing toolbox. *Chemical Senses.* 2018;43(8):583-597.
26. González HM, Mungas D, Reed BR, Marshall S, Haan MN. A new verbal learning and memory test for English- and Spanish-speaking older people. *J Int Neuropsychol Soc.* 2001;7(5):544-555.
27. Breton J, Stickel AM, Tarraf W, et al. Normative data for the Brief Spanish-English Verbal Learning Test for representative and diverse Hispanics/Latinos: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Alzheimers Dement (Amst).* 2021;13(1):e12260.
28. Lezak MD, Howieson DB, Loring DW, Fischer JS. *Neuropsychological Assessment.* New York, NY: Oxford University Press; 2004.
29. Wechsler D. *WAIS-R: Manual: Wechsler Adult Intelligence Scale—Revised.* New York, NY: Harcourt Brace Jovanovic for Psychological Corp; 1981.
30. González HM, Tarraf W, Gouskova N, et al. Neurocognitive function among middle-aged and older Hispanic/Latinos: results from the Hispanic Community Health Study/Study of Latinos. *Arch Clin Neuropsychol.* 2015;30(1):68-77.
31. Gerritsen RJ, Band GP. Breath of life: the respiratory vagal stimulation model of contemplative activity. *Front Hum Neurosci.* 2018;12:397.
32. Herberts M, Kolla B, Paul T, Mekala P, Mansukhani MP. Sleep apnea and autonomic dysfunction in patients with dementia. *Front Neurosci.* 2022;16:951147.
33. Knight EL, Giuliano RJ, Shank SW, Clarke MM, Almeida DM. Parasympathetic and sympathetic nervous systems interactively predict change in cognitive functioning in midlife adults. *Psychophysiology.* 2020;57(10):e13622.
34. Pal A, Martinez F, Akey MA, et al. Breathing rate variability in obstructive sleep apnea during wakefulness. *J Clin Sleep Med.* 2022;18(3):825-833.
35. Gutierrez G, Williams J, Alrehaili GA, et al. Respiratory rate variability in sleeping adults without obstructive sleep apnea. *Physiological Reports.* 2016;4(17):e12949.
36. Ju Y-ES, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid- β levels. *Brain.* 2017;140(8):2104-2111.
37. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol.* 2013;177(9):1006-1014.
38. Lowe CJ, Safati A, Hall PA. The neurocognitive consequences of sleep restriction: a meta-analytic review. *Neurosci Biobehav Rev.* 2017;80:586-604.