

Sleep-Disordered Breathing and Cognitive Decline in Older Adults

Nicola Canessa, PhD

Luigi Ferini-Strambi, MD

SLEEP-DISORDERED BREATHING HAS BEEN ASSOCIATED with declines in memory, attention, and executive functions in both middle-aged adults and children, with intermittent hypoxemia and fragmented sleep patterns being the factors most frequently associated with decline.¹ In elderly patients, some studies have found a relationship between cognitive impairment and sleep-disordered breathing,^{2,3} while others have not.^{4,5} However, conflicting results may be explained by methodological differences across these studies that assessed longitudinal data in elderly individuals,² cross-sectional data from young and elderly individuals³ or only elderly individuals,⁵ or direct comparisons between younger and older patients.⁴ Most importantly, cross-sectional studies do not allow conclusions to be drawn regarding causality. Because sleep-disordered breathing is common among older adults and effective treatments for sleep-disordered breathing exist, establishing the possible prospective association between sleep-disordered breathing and cognitive functioning in elderly individuals is important at both theoretical and practical levels. The article by Yaffe et al⁶ in this issue of *JAMA* helps to clarify this association.

Yaffe et al⁶ aimed to determine the prospective relationship between sleep-disordered breathing and cognitive impairment as well as the potential underlying mechanisms in a sample of 298 women without dementia. Overnight in-home polysomnography provided data on hypoxia, sleep-fragmentation, and sleep duration at the study baseline, while cognitive assessment (normal, mild cognitive impairment, or dementia) was performed approximately 5 years later via neuropsychological tests and subsequent evaluation by a panel of clinical experts. In a multivariate logistic regression adjusting for age, body mass index, education level, presence of diabetes, and baseline cognitive scores, sleep-disordered breathing was associated with development of cognitive impairment (odds ratio, 1.85; 95% confidence interval, 1.11-3.08). Measures of intermittent hypoxia (oxy-

gen desaturation index and high percentage [$>7\%$] of sleep time in apnea or hypopnea) were associated with mild cognitive impairment or dementia, suggesting that hypoxia is a likely mechanism through which sleep-disordered breathing increases risk for cognitive impairment.

Yaffe et al⁶ also found that sleep fragmentation (arousal index and wake after sleep onset) or sleep duration (total sleep time) were not associated with risk of mild cognitive impairment or dementia. However, their study focused on older women. It has been reported that the effects of sleep fragmentation on performance are more clear-cut in younger than in older individuals,⁷ and that healthy elderly adults tolerate sleep deprivation better than young adults.⁸ Although these results were obtained in acute experimental conditions, older adults appear somewhat less sensitive than young adults to sleep fragmentation or sleep reduction in other settings.

Moreover, individuals may adapt to long-term sleep changes as suggested by data on patients with restless legs syndrome and periodic limb movements. Restless legs syndrome is a common sensorimotor disorder that peaks in severity during the night, and usually results in significant chronic sleep loss. Moreover, among patients with restless legs syndrome, periodic limb movements increase the arousal index. When cognitive functioning in patients with restless legs syndrome was compared with normal sleep-restricted controls,⁹ patients with restless legs syndrome performed better than sleep-restricted controls on 2 tasks that are particularly sensitive to sleep loss, letter fluency and category fluency. This result suggests that patients with chronic sleep changes may have a relative degree of sleep loss adaptation, which may not be the case for hypoxia. Thus, the finding by Yaffe et al⁶ that hypoxia but not sleep fragmentation is associated with mild cognitive impairment or dementia is supported by prior research.

Because hypoxia may mediate the association of sleep-disordered breathing with mild cognitive impairment or dementia, Yaffe et al⁶ reported that their findings suggest a po-

Author Affiliations: Center for Cognitive Neuroscience (Dr Canessa), Università Vita-Salute San Raffaele (Dr Ferini-Strambi), Milan, Italy; and Division of Neuroscience (Drs Canessa and Ferini-Strambi) and Sleep Disorders Center (Dr Ferini-Strambi), San Raffaele Scientific Institute, Milan, Italy.

Corresponding Author: Luigi Ferini-Strambi, MD, Sleep Disorders Center, Vita-Salute San Raffaele University, Italy (ferinistrambi.luigi@hsr.it).

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tential role for supplemental oxygen therapy for sleep-disordered breathing in elderly individuals and recommend further study. In some patients with sleep-disordered breathing who cannot tolerate treatment with continuous positive air pressure (CPAP), and who are not candidates for a surgical procedure, supplemental oxygen therapy is sometimes administered to reduce the harmful effects of transient desaturations during sleep.¹⁰ However, supplemental oxygen as a therapy for sleep-disordered breathing and its effect on neuropsychological functioning have not been extensively evaluated, while potential dangers (eg, prolongation of apnea duration, increased hypercarbia and acidosis, and increased ventricular irritability) should be considered.¹¹ As noted by Yaffe et al,⁶ trials treating patients with Alzheimer disease and sleep-disordered breathing with CPAP have shown the treatment to slow or even improve cognitive impairment.^{12,13} No medications are known to prevent the progression of mild cognitive impairment to Alzheimer disease or dementia,¹⁴ so treating at-risk patients with CPAP for sleep-disordered breathing is a prevention strategy that may be worth testing.

Use of CPAP to treat patients with sleep-disordered breathing to slow cognitive decline would be consistent with research suggesting common underlying neural mechanisms relating hypoxia and mild cognitive impairment. In a study using voxel-based morphometry, the cognitive and neurological deficits associated with obstructive sleep apneas, mainly involving memory, attention, and executive functioning (associated with decreased hippocampal gray matter), were improved after treatment with CPAP.¹⁵ The hippocampus is one of the main and most consistently reported brain regions among the neural correlates of mild cognitive impairment as shown by a recent meta-analysis.¹⁶ Despite the clear differences between the pathology of the populations investigated in these studies, the hippocampal cortex appears to be involved with both hypoxia and mild cognitive impairment. The study by Yaffe et al⁶ nicely links this phenomenon.

In conclusion, the study by Yaffe et al⁶ and related studies to date suggest that large trials with CPAP treatment in elderly participants with sleep-disordered breathing should be performed. Moreover, in trials evaluating the effects of pharmacological and nonpharmacological (eg, cognitive training and rehabilitation) interventions on cognitive function in patients with mild cognitive impairment or dementia, the possible coexistence of sleep-disordered breathing

should be considered. Finally, physicians of patients with mild cognitive impairment and sleep-disordered breathing for whom treatment with CPAP may be indicated should consider these results, and future guidelines to formalize the clinical management of patients with mild cognitive impairment¹⁷ should consider the implications of this study and related research.

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ferini-Strambi reported that he is a board member for Boehringer Ingelheim, UCB-Pharma, GlaxoSmithKline, and sanofi-aventis. No other disclosures were reported.

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