International Psychogeriatrics (2023), 35:8, 403–406 © International Psychogeriatric Association 2023
doi:10.1017/S1041610223000030

COMMENTARY

Association between sleep disturbances and mild cognitive impairment: Clinical and research considerations

Commentary on "Late-life sleep duration associated with amnestic mild cognitive impairment" by Yuan *et al.*

Joshua M. Baruth,[1] Manuel Fuentes Salgado,[1] Boney Joseph,[2] Balwinder Singh,[1] and Nicolas A. Nunez[1]

[1]*Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA*
[2]*Department of Neurology Mayo Clinic, Rochester, MN, USA*
Email: nunez.nicolas@mayo.edu

Over the last few decades, there has been increasing interest in understanding the potential relationship between sleep disturbances and cognitive decline. Specifically, changes in sleep duration and onset of mild cognitive impairment (MCI) has been investigated as it may provide potential opportunities for early identification of subjects and/or treatment interventions (Basta *et al.*, 2019; Wang *et al.*, 2021). The clinical presentation of MCI can be quite heterogeneous and represents a state between normal aging and dementia which obscures the diagnosis frequently. A general consensus for defining MCI includes the presence of early measurable deficits in at least one cognition domain in the absence of functional impairments without meeting criteria for dementia (APA, 2013; Ganguli *et al.*, 2004).

The emergence of MCI is common in older adults, and data from the American Academy of Neurology has estimated prevalence rates up to 15% in patients older than 75 years (Petersen *et al.*, 2018). Several risk factors have been highly associated with MCI such as male sex, lower educational levels, comorbid medical conditions (chronic lung disease, hypertension, and vascular risk factors), presence of neuropsychiatric symptoms, and the presence of an APOE genotype (Ganguli *et al.*, 2004; Kryscio *et al.*, 2006; Petersen *et al.*, 2018; Singh *et al.*, 2014). Similarly, a greater risk of developing dementia has been associated with increased age, hypertension, smoking habits, obesity, depression, diabetes, and social isolation (Mehta and Yeo, 2017). Notably, studies have shown evidence that over a 5- to 10-year period after a diagnosis of MCI, 30% to 50% of subjects progressed to develop Alzheimer's disease (AD) (Liss *et al.*, 2021).

Neuroimaging studies and several biomarkers acting as disease proxy have been identified, suggesting possible associations on serum levels of melatonin, cortisol, cholesterol, growth hormone, or thyroid-stimulating hormone with sleep disturbances and cognitive decline (Li *et al.*, 2018). These findings highlight the importance of further investigating potential relationships between cognitive decline, sleep changes,and changes in biomarker levels, which could improve early diagnosis and tailor early interventions. Moreover, the presence or absence of specific candidate genes such as frequency of the APOEϵ4 allele, APP, presenilin 1 (PSEN1), presenilin 2 (PSEN2), SORL1, and potentially others such as TLR4, CHRNB2, A2M, CTNNA3, GSTO1, GSTO2, GAPD, and ACT (Arosio *et al.*, 2007) remain to be investigated as risk factors for MCI and AD which could provide a better understanding of structural and functional neuroimaging findings in correlation with clinical features.

Sleep disturbances in general affect at least one-third of patients with dementia, and specifically, insomnia is the most commonly reported symptom (Morin and Benca, 2012); up to 50% of older adults complain of difficulty initiating or maintaining sleep (Crowley, 2011). Foley and colleagues emphasized a high prevalence of at least one or more comorbid medical conditions in elderly individuals with insomnia such as cardiovascular disease, chronic pain, respiratory disease, and depression (Foley *et al.*, 1995). Thus, a possible bidirectional relationship has been suggested between sleep disturbances

and dementia, with an increase in overall sleep disturbances in patients with dementia compared to healthy individuals (Bliwise, 2004). Additionally, different studies have reported changes in sleep latency, sleep efficiency, and sleep stage duration, with increases in stage 1 and stage 2 and decreases in REM and slow wave sleep with increasing age (Ohayon *et al.*, 2004; Pótári *et al.*, 2017); particularly, Ohayon and colleagues have suggested a decrease in total sleep time ranging from 5 to 7 hours per night in older adults (Ohayon *et al.*, 2004). In this context, a lower average of sleep efficiency, longer average sleep latency, and greater variability in total sleep time have been associated with greater risk of cognitive decline (Diem *et al.*, 2016). Therefore, sleep duration as a proxy may constitute an early indicator of future risk of cognitive decline which could also be a modifiable risk factor during midlife (45 to 65 years of age) capable of reducing the increasing incidence of dementia cases.

Yuan *et al.* in their cross-sectional findings published in *International Psychogeriatrics* extend prior findings related to sleep changes in older adults by investigating the relationship between sleep changes and risk of MCI. The authors examined data from the China Longitudinal Aging Study of the Shanghai Mental Health Centre collected from eight provinces (N = 2977, age range 60–96 years). Among older adults sleeping less than 7 hours, there was a decreased risk of amnestic MCI for each additional hour of sleep (Yuan *et al.*, 2021) which aligns with previous studies, all having considerable public health implications (Dorffner *et al.*, 2015; Ohayon *et al.*, 2004; Vitiello *et al.*, 2004a).

Yuan *et al.* emphasized the importance of examining sleep duration and its relationship with cognitive decline (Yuan *et al.*, 2021). Nevertheless, different studies have been inconsistent in determining whether increased or decreased sleep duration is associated with a higher risk of MCI or dementia. For example, a meta-analysis of five prospective studies and four cross-sectional studies (N = 62937 individuals/n = 2718 with MCI/dementia) underscored a higher risk of cognitive decline per 1 hour increase in sleep duration (Kim *et al.*, 2016). Importantly, a longer sleep duration (>9 hours) has been associated with lower brain volumes and higher executive function impairments and could constitute a biological marker of early neurodegeneration (Westwood *et al.*, 2017). In accordance with these results, a prospective study published in the *International Psychogeriatrics by* Zhang and colleagues examining a cohort with a 3-year follow-up duration from the Chinese Longitudinal Healthy Longevity Survey (N = 3692) has shown that long sleep duration ($\geq$ 10 hours/day) may be associated with a higher risk for cognitive impairment in older individuals (OR = 1.3 95% CI 1.1–1.7) in comparison with short sleep duration (5–10 hours/day).

Conversely, a shorter sleep duration (< 6 hours per night) has been emphasized by Ma *et al.* and the recent published study by Yuan *et al.*, which emphasize an association between cognitive decline and reduced sleep duration (Ma *et al.*, 2020). The Ma *et al.* study comprised a pooled cohort of two large observational studies, 9,254 participants from the English Longitudinal Study of Ageing and 10,811 participants from the China Health and Retirement Longitudinal Study. Specifically, there was an association between insufficient sleep ($\leq$ 4 hours) or excessive ($\geq$ 10 hours) sleep with cognitive decline. Similarly, Sabia and colleagues using data from the Whitehall II study (N = 7959) during a 25-year-follow-up period demonstrated a 30% increased risk of dementia associated with persistent short sleep duration in subjects aged 50–70 years of age after controlling for comorbid medical conditions and sociodemographic factors (Sabia *et al.*, 2021). Importantly, a recent longitudinal study involving 1168 older adults (>50 years of age) without AD symptoms at baseline from the European Prevention of Alzheimer's Dementia Longitudinal Cohort reported associations between AD biomarkers (total tau [t-tau], phosphorylated tau [p-tau], and amyloid-beta) in cerebrospinal fluid, cognitive performance, and sleep quality. Notably, the authors showed that sleeping less than 7 hours was linked with higher p-tau and t-tau and decreased Aβ42 after 1.5 years (Blackman *et al.*, 2022).

Although the Yuan *et al.* study utilized subject's self-report as a measure of sleep duration which was verified by family members, however, the possibility of recall bias cannot be ruled out (Yuan *et al.*, 2021). Prior studies have shown that subjective reports of older adults regarding sleep are not fully accurate compared to objective measures (Vitiello *et al.*, 2004b). In particular, the inclusion of self-reported data based on recollection of sleep duration would likely be even more subject to recall bias in different age groups (younger and middle-aged adults) as well as for different countries (Spitzer and Weber, 2019). Additionally, including more granular measures of cognitive function like episodic memory, semantic memory, working memory, and processing speed could better characterize the relationship between sleep changes and decline in individual cognitive domains and is warranted in future study designs.

Therefore, future research considering the impact of ethnic background and diversity could increase studies generalizability as it has been addressed in a commentary published recently in the *International Psychogeriatrics* by Kuan and Lee (Kuan and Lee, 2022). Moreover, Wright and colleagues examining data from a racial and ethnically diverse population showed that there was higher incidence of MCI or

https://doi.org/10.1017/S1041610223000030 Published online by Cambridge University Press

dementia in Black and Caribbean Hispanics compared to Whites after controlling for sociodemographic and medical comorbidities (Wright *et al.*, 2021).

The influence of mood disorders and associations between depression, cognitive impairment, and dementia have also been studied extensively and should be mentioned in this context (Woolley *et al.*, 2011). A systematic review and meta-analysis reported that a history of bipolar disorder was associated with a two-times-greater risk of dementia in older adults (Diniz *et al.*, 2017). Additionally, depressive symptoms, particularly late-life depression, have been associated as a risk factor for developing dementia; similarly, subjective cognitive decline has been associated with the emergence of MCI and dementia increasing the risk up to 4 and 6 times compared to healthy individuals (Wang *et al.*, 2021). Therefore, it should also be noted that lifetime psychiatric disorders (e.g. affective disorders) can increase the risk for cognitive impairments, sleep disturbances, and neurodegenerative disorders and should be weighted in our differential diagnosis. Importantly, quantifying the role of psychiatric illnesses to cognitive decline and potentially dementia could enhance early prevention and diagnosis strategies.

Overall, the Yuan *et al*. study highlights an unmet need to better characterize associations between sleep duration and risk for cognitive decline. As mentioned, including more granular measures like objective sleep outcomes, biomarkers, cognitive domains, neuroimaging, medication use, and genetic risk factors has the potential to improve the design of longitudinal/observational studies. Importantly, the development of risk stratification models could contribute to earlier identification of modifiable risk factors of cognitive decline and potential for targeted interventions, in the aging population.

Conflict of interest

Dr Singh reports grant support from Mayo Clinic.

Description of authors' roles

The authors Joshua M. Baruth, Manuel Fuentes Salgado, Boney Joseph, Balwinder Singh, and Nicolas A. Nunez equally contributed to the manuscript and revised, read, and approved the submitted version.

Acknowledgment

We would like to thank Ms. Lori Solmonson and Ms. Rene Kelly-Jambor for proofreading the manuscript and writing support.

References

APA (2013). Diagnostic and statistical manual of mental disorders. *American Psychiatric Association*, 21, 591–643.

Arosio, B., *et al.* (2007). PIN-1 promoter polymorphisms in mild cognitive impairment and susceptibility to Alzheimer's disease: a preliminary report. *Aging Clinical and Experimental Research*, 19, 406–409.

Basta, M., *et al.* (2019). Associations between sleep duration and cognitive impairment in mild cognitive impairment. *Journal of Sleep Research*, 28, e12864.

Blackman, J., *et al.* (2022). Cross-sectional and longitudinal association of sleep and Alzheimer biomarkers in cognitively unimpaired adults. *Brain Communications*, 4, fcac257.

Bliwise, D. L. (2004). Sleep disorders in Alzheimer's disease and other dementias. *Clinical Cornerstone*, 6, S16–S28.

Crowley, K. (2011). Sleep and sleep disorders in older adults. *Neuropsychology Review*, 21, 41–53.

Diem, S. J., *et al.* (2016). Measures of sleep–wake patterns and risk of mild cognitive impairment or dementia in older women. *The American Journal of Geriatric Psychiatry*, 24, 248–258.

Diniz, B. S., *et al.* (2017). History of bipolar disorder and the risk of dementia: a systematic review and meta-analysis. *The American Journal of Geriatric Psychiatry*, 25, 357–362.

Dorffner, G., Vitr, M. and Anderer, P. (2015). The effects of aging on sleep architecture in healthy subjects. *Advances in Experimental Medicine and Biology*, 821, 93–100. https://doi.org/10.1007/978-3-319-08939-3_13

Foley, D. J., Monjan, A. A., Brown, S. L., Simonsick, E. M., Wallace, R. B. and Blazer, D. G. (1995). Sleep complaints among elderly persons: an epidemiologic study of three communities. *Sleep*, 18, 425–432.

Ganguli, M., Dodge, H. H., Shen, C. and DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology*, 63, 115–121.

Kim, H. K., Nunes, P. V., Oliveira, K. C., Young, L. T. and Lafer, B. (2016). Neuropathological relationship between major depression and dementia: a hypothetical model and review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 67, 51–57.

Kryscio, R., Schmitt, F., Salazar, J., Mendiondo, M. and Markesbery, W. (2006). Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology*, 66, 828–832.

Kuan, R. and Lee, E. (2022). The importance of diversity in aging studies. *International Psychogeriatrics*, 34(8), 683–685. https://doi.org/10.1017/S1041610222000217

Li, J., Vitiello, M. V. and Gooneratne, N. S. (2018). Sleep in normal aging. *Sleep Medicine Clinics*, 13, 1–11.

Liss, J., *et al.* (2021). Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis. *Journal of Internal Medicine*, 290, 310–334.

Ma, Y., Liang, L., Zheng, F., Shi, L., Zhong, B. and Xie, W. (2020). Association between sleep duration and cognitive decline. *JAMA Network Open*, 3, e2013573–e2013573.

Mehta, K. M. and Yeo, G. W. (2017). Systematic review of dementia prevalence and incidence in United States race/ethnic populations. *Alzheimer's & Dementia*, 13, 72–83.

https://doi.org/10.1017/S1041610223000030 Published online by Cambridge University Press

Morin, C. M. and Benca, R. (2012). Chronic insomnia. *The Lancet*, 379, 1129–1141.

Ohayon, M. M., Carskadon, M. A., Guilleminault, C. and Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*, 27, 1255–1273.

Petersen, R. C., *et al.* (2018). Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*, 90, 126–135.

Pótári, A., *et al.* (2017). Age-related changes in sleep EEG are attenuated in highly intelligent individuals. *Neuroimage*, 146, 554–560.

Sabia, S., *et al.* (2021). Association of sleep duration in middle and old age with incidence of dementia. *Nature Communications*, 12, 1–10.

Singh, B., *et al.* (2014). A prospective study of chronic obstructive pulmonary disease and the risk for mild cognitive impairment. *JAMA Neurology*, 71, 581–588.

Spitzer, S. and Weber, D. (2019). Reporting biases in self-assessed physical and cognitive health status of older Europeans. *Plos one*, 14, e0223526.

Vitiello, M. V., Larsen, L. H. and Moe, K. E. (2004a). Age-related sleep change: gender and estrogen effects on the subjective–objective sleep quality relationships of healthy, noncomplaining older men and women. *Journal of Psychosomatic Research*, 56, 503–510.

Vitiello, M. V., Larsen, L. H. and Moe, K. E. (2004b). Gender and estrogen effects on the subjective-objective sleep quality relationships of healthy, noncomplaining older men and women. *Journal of Psychosomatic Research*, 56, 503–510.

Wang, S.-M., *et al.* (2021). Late-life depression, subjective cognitive decline, and their additive risk in incidence of dementia: a nationwide longitudinal study. *Plos one*, 16, e0254639.

Westwood, A. J., *et al.* (2017). Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia. *Neurology*, 88, 1172–1179.

Woolley, J. D., Khan, B. K., Murthy, N. K., Miller, B. L. and Rankin, K. P. (2011). The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *The Journal of Clinical Psychiatry*, 72, 4437.

Wright, C. B., DeRosa, J. T., Moon, M. P., Strobino, K., DeCarli, C., Cheung, Y. K., Assuras, S., Levin, B., Stern, Y., Sun, X., Rundek, T., Elkind, M. S. V. and Sacco, R. L. (2021). Race/ethnic disparities in mild cognitive impairment and dementia: the Northern Manhattan study. *Journal of Alzheimer's Disease: JAD*, 80(3), 1129–1138. https://doi.org/10.3233/JAD-201370

Yuan, M., *et al.* (2021). Late-life sleep duration associated with amnestic mild cognitive impairment. *International Psychogeriatrics*, 35, 439–448. https://doi.org/10.1017/S1041610221000466

https://doi.org/10.1017/S1041610223000030 Published online by Cambridge University Press