Editorial

Comment on "Sleep disturbances and later cognitive status: a multi-centre study"

Roberto Monastero, Roberta Baschi

Department of Experimental Biomedicine and Clinical Neurosciences, Section of Neurology, University of Palermo, Palermo, Italy

Correspondence to: Roberto Monastero, MD, PhD. Associate Professor of Neurology, Department of Experimental Biomedicine and Clinical Neurosciences, Section of Neurology, University of Palermo, Italy, Via La Loggia 1, 90129 Palermo, Italy.

Email: roberto.monastero@unipa.it or roberto.monastero@gmail.com.

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Alzheimer's disease (AD) is the main cause of dementia, and age is the best-known risk factor leading to an increase in the prevalence of the disease with ageing populations worldwide (1). Aging is a complex process leading to chronic inflammation and deterioration of the immune function (2), which results in a worsening of the quality of sleep and in an increase in the prevalence of sleep disorders (3). Normal ageing is also characterized by decreased capability to initiate and maintain sleep, which is associated with a decrease in the proportion of slow wave sleep and rapid eye movement (REM) sleep. Sleep patterns are rather heterogeneous, probably due to changes in circadian and homeostatic processes (4).

Sleep disturbance seems to be associated with systemic inflammation and specifically with its two markers: C-reactive protein and interleukin 6. The latter induces the former, with an increase in C-reactive protein, which was also found in persistent or severe sleep abnormalities. Contrarily, no association has been observed between sleep disturbances with tumor necrosis factor, a proinflammatory cytokine, which appears to be a prominent ligand for the activation of programmed cell death through apoptosis (5). Different types of sleep disturbances can occur in the elderly; these typically include insomnia, sleep disordered breathing (SDB), and other sleep problems (excessive daytime sleepiness, sleep-related movement disorder, circadian rhythm sleep disorder, and nonspecific sleep problems) (3).

Sleep plays an important role in cognitive processing, and changes in sleep quality (i.e., long sleep duration and insomnia) can lead to impairments in cognitive performance, which have been linked to an increased risk in cognitive impairment and dementia in various longitudinal studies (6,7). Furthermore, the severity of sleep disruption was associated with the severity of dementia (8).

Chronic sleep deprivation in mouse models of AD has been demonstrated to increase amyloid plaque formation (6). In preclinical AD [i.e., cognitively normal individuals with low cerebrospinal fluid β-amyloid 42 (Aβ42) levels], amyloid deposition was associated with poor sleep quality (9). Furthermore, subjects in the prodromal phase of AD, the so-called mild cognitive impairment (MCI) (10) who show significant changes in plasma Aβ levels, displayed disrupted slow-wave sleep with concomitant increased plasma levels of Aβ42 (11). REM sleep abnormalities in this study significantly related with a thinning of the bilateral postcentral gyrus and left posterior cingulate cortex. This evidence suggests that sleep may influence the AD-type neurodegenerative process, probably causing a disruption in sleep-wake mechanisms in specific cortical areas.

Epidemiological evidence deriving from a population-based, Swedish, longitudinal study showed that reduced sleep was associated with a 75% increase in all-cause dementia risk, thereby doubling the risk of AD (12). During a 40-year observational period (13), reports of sleep disturbance, in particular initial and terminal insomnia, in

initially cognitively healthy men were associated with an increased risk of developing all-cause dementia. In addition, in order to obtain an objective measure of sleep disturbance and to reflect overall health status, Sterniczuk *et al.* created a "Sleep Disturbance Index". They observed that this index was associated with a 23% increased risk of developing AD or dementia and 18% increased risk of mortality (14).

The majority of studies, which have evaluated sleep disturbances in dementia, have used self-reported symptoms or questionnaires to define sleep disturbance while very few have objectively used monitored sleep parameters. In the Framingham Heart Study Offspring cohort, an overnight polysomnography was performed, and shorter REM sleep percentages and longer REM latencies were found to be significantly associated with an increased risk of all-cause dementia (15). Moreover, the authors of this study found that the lowest *vs.* highest tertile of REM sleep latencies and higher total sleep time were associated with a lower risk of all-cause dementia, while higher wake after sleep onset was associated with an increased risk of incident all-cause dementia. Lastly, sleep onset latency, sleep efficiency, and the apnea-hypopnea index were not found to be related to the incidence of dementia.

Another recent longitudinal study found that late-midlife obstructive sleep apnea (OSA) and short sleep duration were associated with all-cause dementia and AD in later life (16). After adjusting for cardiovascular risk factors, the magnitude of this association decreased, probably because the effect of OSA on dementia is mediated by cardiovascular comorbidity. Sleeping less than 7 hours/night was associated with a twofold higher risk of all-cause dementia.

Few prospective population-based cohort studies have evaluated sleep disturbances in MCI. A prospective sleep and cognition sub-study of the Study of Osteoporotic Fractures conducted on women with SDB (who had undergone an overnight polysomnography) demonstrated that these subjects were at an increased risk of developing MCI or dementia (17). Specifically, measures of hypoxia were associated with an increased risk of developing MCI and dementia, while measures of sleep fragmentation and sleep duration were not. In another prospective study of over 7,400 community-dwelling women from the Women's Health Initiative Memory Study, the authors found that the hazard for MCI/dementia was increased by nearly 35% in women with an either short (≤6 hours/night) or long (≥8 hours/night) sleep duration *vs.* those subjects who sleep 7 hours/night (18).

Overall, cognitive impairment syndromes are potentially susceptible to prevention through clinical intervention and behavioural modifications. Thus, understanding the link between dementia and sleep may contribute to the development of effective prevention strategies. However, very few longitudinal studies have evaluated sleep disturbances using large sample size, long-term follow-up, and considering multiple potential confounders.

The work by Sindi *et al.* (19) has specifically aimed at answering these questions, which have hitherto lain unsolved. This study included data from three population-based, prospective cohort studies from Nordic countries with an overall sample of over 1,400 male and female subjects. The authors conducted midlife and late-life baseline analyses and controlled for several relevant confounders. Specifically, the subjects in the study were drawn from three population-based prospective studies: the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study, the H70 study and the Kungsholmen Project (KP), which have been conducted in Finland and Sweden. The main aims of the study were: (I) to examine the role of insomnia in midlife and late-life and the risk of dementia; (II) to evaluate the subjective ratings of reduced sleep duration or depth in late-life; and (III) to assess the role of sleep duration (in hours) in late-life and their association with dementia. The three studies included different follow-up times (mean follow-up: CAIDE study 21 years, H70 study about 10 years, and KP 9 years), thus permitting the stratification of analyses in long- (21–32 years) and short- (3–9 and 5-10 years) term follow-up.

The sleep disturbances reported in the work by Sindi *et al.* were assessed by means of self-reported symptoms or questionnaires, evaluating insomnia in midlife, terminal and initial insomnia in late-life, sleep quality/quantity, and sleep duration. A diagnosis of dementia was performed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (DSM-IV in CAIDE; DSM-IIIR in H70 and KP) (20). In all three studies, the survey methods were standardised and the authors included the following covariates: socio-demographic factors, alcohol consumption, physical activity, cohabitant status, vascular diseases/disorders, use of hypnotics, self-reports of depression and apolipoprotein 4 (APOE) ε4 genotype.

In the long-term follow-up analyses, the authors found that midlife insomnia was associated with a higher risk for dementia with a multi-adjusted hazard ratio of 1.24. Terminal insomnia in late-life (adjusted odds ratio =1.94) and long sleep duration (more than 9 hours, adjusted odds ratio =3.98) in the short-term follow-up analyses were

associated with an increased risk of dementia, while no association was found for initial insomnia, reduced sleep, and short sleep duration in late-life.

Although the authors used long-term follow-up analyses from multiple population-based studies, evaluated different sleep dimensions and adjusted for multiple confounders, the article by Sindi *et al.* has some limitations, as the authors acknowledged in the Discussion section of the article. First, it lacks an objective measurement of sleep. Indeed, the objective analysis of sleep architecture in normal and pathological aging is useful for understanding the biological mechanisms underlying different sleep disturbances and for identifying possible targets for clinical intervention (8). Second, the authors only covariate for the use of hypnotics, while details regarding other medications were unavailable. Different medications, such as antihypertensive drugs (alfa and beta-blockers), corticosteroids, and those for the treatment of dementia (e.g., rivastigmine) could affect sleep architecture (21). Accordingly, including these variables in the analysis would reduce confounding, thereby conferring additional data robustness. Third, the authors neither used standardised diagnostic criteria for depression nor did they evaluate other behavioural disturbances affecting sleep pattern in the elderly with dementia, such as anxiety and psychosis (22), only relying on self-report depression measures. The latter may have led to recall bias with inherent problems with confounding. Overall, the lack of standardised assessment of behavioural symptoms in the three studied cohorts may have resulted in an underestimation in the accuracy of the association between sleep disturbance and dementia. Lastly, the authors did not stratify their analysis according to dementia subtypes (e.g., Alzheimer's *vs.* vascular dementia). Accordingly, the putative aetiology of sleep disturbance in dementia cannot be inferred from these results.

In conclusion, sleep disturbances are rather frequent in the elderly, and recent investigations suggest that sleep abnormalities increase the risk of MCI and dementia (6,7). Accordingly, sleep disturbances in the elderly should always be carefully investigated using standardised patient- and informant-based instruments in any clinical setting. Evidence from molecular studies has suggested that sleep may influence AD-related neuropathology, probably due to sleep-wake fragmentation in specific cortical areas (9,23). Considering abnormal changes in the molecular inflammatory pathway in individuals with sleep disturbances (5), a plasma level analysis of inflammatory markers and its relationship with disease progression should be investigated as it represents a target for clinical intervention. Lastly, the analysis of sleep organization in individuals in the preclinical phase of dementia/AD, the so-called subjective cognitive decline (SCD) (24), should be performed in order to evaluate if SCD is a possible consequence of altered sleep architecture. For example, Tsapanou *et al.* observed in recent research that increased sleep problems were associated with increased SCD after adjustment for demographics, clinical factors and global cognition (25).

Longitudinal, population-based studies with objective sleep assessment, objective cognition measurement, comprehensive evaluation of comorbidity and medication, and the use of structural magnetic resonance imaging and AD-related biomarkers will clarify the direction of the association between sleep and cognitive impairment of AD-type, particularly in its preclinical phase. Lastly, the relationship between other neuropathological aetiologies (i.e., vascular, a-synuclein and tau-related) and sleep architecture in the elderly with cognitive impairment should be investigated. The answers to all these research questions indicate relevant clinical and prognostic implications for dementia prevention and treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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