Received: 4 September 2022 | Accepted: 7 September 2022

DOI: 10.1111/ene.15562

european journal of neurology
the official journal of the european academy of neurology

COMMENTARY

# Sleep disorders and increased risk of dementia

**Luigi Ferini-Strambi**

Sleep Disorders Center, Università Vita-Salute San Raffaele, Milan, Italy

**Correspondence**
Luigi Ferini-Strambi, Sleep Disorders Center, Università Vita-Salute San Raffaele, via Stamira d'Ancona 20, Milan, 20127, Italy.
Email: ferinistrambi.luigi@hsr.it

There is accumulating evidence linking sleep disturbances with the development of dementia. A 2018 meta-analysis of 18 prospective studies that considered 246,786 individuals in different countries (United States, Europe and Asia) showed that, over an average follow-up of 9.5 years, subjects with sleep disturbance at baseline had a higher risk of incident all-cause dementia compared with those not reporting disturbed sleep [1]. A complaint of insomnia was associated only with incident Alzheimer's disease (AD), while sleep disordered breathing (SDB) was a risk factor for all-cause dementia, including vascular dementia (VD). Could poor sleep be considered a modifiable risk factor for dementia? Several risk factors are non-modifiable: older age, female gender, family history, severe traumatic brain injury, and predisposing genetic mutations. However, it has been reported that modifying 12 identified risk factors, including depression, physical inactivity, midlife untreated hypertension, obesity, tobacco use, and diabetes mellitus might prevent or delay up to 40% of dementias [2]. The study by Damsgaard et al. [3] could facilitate the inclusion of sleep disturbance among the modifiable risk factors for dementia. Their study was a nationwide cohort study that evaluated the association between sleep disorders diagnosed after age 50 years in the secondary healthcare sector and subsequent late-onset dementia. In the cohort of 1,491,276 people, subjects with any sleep disorder had a 17% higher risk of dementia compared to those with no sleep disorder. Interestingly, the risk of dementia was significantly increased in the first 5 years after sleep disorder diagnosis, while the association after 5 years was nonsignificant. Damsgaard et al. [3] distinguished different categories of sleep disorder diagnosis: any sleep disorders; narcolepsy; sleep apnea, other specific disorders; and unspecified disorders. The risk was statistically significant in analyses for all categories only for men: this is probably due to sleep apnea being the most prevalent sleep disorder in the cohort, with this being more frequently diagnosed in men than women. However, one challenge in this field is to explain the differences in the sex distribution of SDB (predominantly affecting men) and, for example, AD (more frequent in women). Women less frequently have moderate-to-severe SDB than men, but they might experience the adverse effects of sleep apnea more than men: they have more fragmented sleep and more frequently report insomnia [4]. Further studies on SDB as a risk factor for dementia should be planned, evaluating sex-based differences in terms of polysomnographic findings, clinical presentation, and consequences.

In the study by Damsgaard et al.[3], out of a population of 1.5 million people, only 615 subjects had an insomnia diagnosis. However, insomnia is very rarely the main reason for a hospital contact because it is usually managed in the primary care setting. Insomnia has been reported to be related to a systemic inflammation process through the activation of microglial cells, thereby resulting in β-amyloid (Aβ) accumulation. Moreover, changes in cerebral blood perfusion and systemic inflammation related to insomnia can promote small vessel disease and ischemic phenomena, thus increasing the risk of VD. A recent study, which used the National Health Insurance Service database covering the entire population of the Republic of Korea from 2007 to 2014, evaluated 2,796,871 patients aged 40 years or older with insomnia [5]. The incidence rate ratios (IRRs) for AD and VD were 1.73 and 2.10, respectively, in patients with insomnia compared to those without. Higher IRRs for AD and VD were observed in men than in women. This finding suggests a need for further studies to assess gender influence in the relationship between insomnia and dementia risk. Moreover, in the evaluation of neurodegenerative risk, differentiating insomnia subtypes may also have a role. A recent Canadian population-based study showed that, compared to maintenance insomnia, subjects with sleep-onset insomnia have more objective cognitive dsyfunction [6].

See paper by L. Damsgaard et al. on page 3528.

Unfortunately, Damsgaard et al. [3] were unable to consider sleep duration and the sleep architecture data in their study. Recently, it has been reported that sleep duration of 6 h or less at age 50 and 60 years is associated with higher risk of dementia. Moreover, a cross-sectional study that evaluated amyloid positron emission tomography and sleep duration in 4425 cognitively unimpaired participants showed that the increased risk of Aβ deposition with reduced nighttime sleep duration occurred early, before cognitive impairment or significant Aβ deposition [7].

Concerning sleep architecture, a reduction in slow wave sleep (SWS) might induce glymphatic system damage. The glymphatic system is almost exclusively active during SWS, and this suggests that treatments that increase SWS should be encouraged. Interestingly, in patients with obstructive sleep apnea the use of positive airway pressure machines increases SWS, and SWS is significantly correlated with lower Aβ levels after treatment. Lastly, body position during sleep could also be crucial for protection against neurodegeneration: in the lateral decubitus position, decreased flow resistance is observed in the extracranial veins, with optimal cerebral venous outflow, which in turn optimizes glymphatic system function [8].

Further studies are needed to clarify the complex relationship between sleep and neurodegeneration, but the data already available indicate, as reported by Damsgaard et al. [3], that "there should be higher focus on sleep disorders as a red flag for possible early phase dementia disorders".

## ACKNOWLEDGEMENT

Open access funding provided by BIBLIOSAN.

## CONFLICT OF INTEREST

LF-S has received speaker fees from Jazz Pharma, Angelini, Valeas, Bioprojet, Fidia, Idorsia and has served on scientific advisory boards for Jazz Pharma, Italfarmaco, Bioprojet, Bayer, Idorsia.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ORCID

*Luigi Ferini-Strambi* https://orcid.org/0000-0003-2867-5424

## REFERENCES

1. Shi L, Chen SJ, Ma MY, et al. Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis. *Sleep Med Rev*. 2018;40:4-16.
2. Gill Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446.
3. Damsgaard L, Laursen T, Erlangsen A, Spira A, Waldemar G. Hospital-diagnosed sleep disorders and incident dementia: a nationwide observational cohort study. *Eur J Neurol*. 2022;29(12):3528-3536. doi:10.1111/ene.15517.
4. Liguori C, Maestri M, Spanetga M, et al. Sleep-disordered breathing and the risk of Alzheimer's disease. *Sleep Med Rev*. 2021;55:101375. doi:10.1016/j.smrv.2020.101375
5. Baek MS, Han K, Kwon H-S, Lee YH, Cho H, Lyoo CH. Risks and prognoses of alzheimer's disease and vascular dementia in patients with insomnia: a nationwide population-based study. *Front Neurol*. 2021;12(62):611446. doi:10.3389/fneur.2021.611446
6. Yao CW, Pelletier A, Fereshtehnejad S-M, Cross N, Dang-Vu T, Postuma RB. Insomnia symptom subtypes and manifestations of prodromal neurodegeneration: a population-based study in the Canadian Longitudinal Study on Aging. *J Clin Sleep Med*. 2022;18(2):345-359.
7. Insel PS, Mohlenhoff BS, Neylan TC, Krystal AD, Mackin RS. Association of sleep and β-amyloid pathology among older cognitively unimpaired adults. *JAMA Netw Open*. 2021;4(7):e2117573. doi:10.1001/jamanetworkopen.2021.17573
8. Simka M, Czaja J, Kowalczyk D. Collapsibility of the internal jugular veins in the lateral decubitus body position: a potential protective role of the cerebral venous outflow against neurodegeneration. *Med Hypotheses*. 2019;133:109397. doi:10.1016/j.mehy.2019.109397