Supplementary Material

Long Objective Sleep Duration Is a Marker of Cognitive Impairment in Older Adults: Findings from the Cretan Aging Cohort

Study design

In this cross-sectional study, we analyzed, a subset of 110 participants from the CAC (Phase III), from a large cohort study conducted on the island of Crete, Greece, who had undergone follow-up within a period of 7–9 years from the initial evaluation (Phase I and II). All participants underwent comprehensive neuropsychological, and neuropsychiatric assessment, along with actigraphy recording during baseline (Phase I and II) and follow-up (Phase III). Approval for the Phase I and II procedures was obtained from the Bioethics Committee of the University Hospital of Heraklion, Crete (Protocol Number: 13541, 20-11-2010), while the current study protocol (Phase III) was approved by the Ethics Committee of the University of Crete (approval number: 61/9-3-2020).

A comprehensive overview of Phases I, II, and III can be found in previous publications [1-3] (Fig. 1). In brief, in Phase I, consenting participants (n=3,200, ≥60 years old) were recruited from selected Health Care Primary settings in Crete and in addition to sociodemographic information, anthropometric measurements and medical history, the Greek version of the Mini-Mental State Examination was administered (with a cut-off score of 23/24 points) [4]. Participants with terminal illnesses and/or movement impairment, missing data and those who declined further participation were excluded. In Phase II, the final cohort consisted of 344 participants with an MMSE score below 24 points, who underwent a comprehensive neuropsychological examination and a control group of 161 participants with an MMSE score of 24 points or higher, matched the low MMSE group in terms of sociodemographic characteristics. Cognitive decline was defined based on the deterioration in diagnosis between the two phases, i.e., cognitively non-impaired at baseline, diagnosed as MCI or dementia at follow up, and MCI at baseline diagnosed as dementia at follow-up. The participants were subsequently categorized into three diagnostic groups: CNI (n = 146), MCI (n = 231), and Dementia (n = 128), based on the diagnostic criteria provided by the International Working Group for MCI diagnosis [5] and the Diagnostic Statistical Manual for Mental Disorders (4th edition). In Phase III all participants who met formal criteria for MCI and

CNI individuals at Phase II were invited to participate. The procedures followed during both Phase II and III phases were the same [3].

Sociodemographic and medical information

At both measurement points, comprehensive records were maintained for anthropometric measurements, comorbidities, use of SSRIs, benzodiazepines, and other anxiolytics. Presence of at least one insomnia-type symptom (i.e., difficulty initiating/maintaining sleep and/or early morning awakening) and sleep apnea was estimated based on the Penn State Sleep Questionnaire [6].

Objective sleep measures

Objective sleep variables were estimated by analyzing consecutive 7-days actigraphy recording at follow-up [7, 3]. The participants were given instructions to wear an actigraph (Actilife v6.9.5, GT3XP model, Pensacola, FL, USA) on their non-dominant hand. They were also required to maintain sleep diaries and record "time in bed," "time out of bed," and any napping periods (>20 min) on a daily basis. The sleep variables estimated were night sleep efficiency (SE), night wake after sleep onset time (WASO), night and 24-h total sleep time (TST) and finally, night and 24-h time spent in bed (TiB). Periods of movement absence that were not logged as sleep periods in sleep diaries were excluded from further examination. Participants with less than 3 days of actigraphy recording and those with relatively short night sleep periods (average night TST < 180 min) were excluded from further analysis. Following our previous publication [8], we categorized the sample into quartiles. We then further divided it into two groups: the long sleep duration group, consisting of the top 25% of individuals with sleep times above the median, and the normal sleep duration group, consisting of the remaining 75% in the lower half.

Neuropsychiatric evaluation

The diagnosis of depression at baseline and follow-up was established by taking into account the use of antidepressants, conducting a clinical interview, and evaluating scores on self-report questionnaires (15-item Geriatric Depression scale and the Center for Epidemiologic Studies Depression Scale), in accordance with the DSM-IV and DSM-V, respectively. The diagnosis of anxiety was established based on clinical evaluation combined with the current use of psychotropic

substances and subjective distress levels (assessed using the anxiety subscale of the Hospital Anxiety Depression Scale).

REFERENCES

[1] Basta M, Simos P, Vgontzas A, Koutentaki E, Tziraki S, Zaganas I, Panagiotakis S, Kapetanaki S, Fountoulakis N, Lionis C (2019) Associations between sleep duration and cognitive impairment in mild cognitive impairment. *J Sleep Res* **28**, e12864.

[2] Zaganas IV, Simos P, Basta M, Kapetanaki S, Panagiotakis S, Koutentaki I, Fountoulakis N, Bertsias A, Duijker G, Tziraki C, Scarmeas N, Plaitakis A, Boumpas D, Lionis C, Vgontzas AN (2019) The Cretan Aging Cohort: cohort description and burden of dementia and mild cognitive impairment. *Am J Alzheimers Dis Other Demen* **34**, 23-33.

[3] Basta M, Skourti E, Alexopoulou C, Zampetakis A, Ganiaris A, Aligizaki M, Simos P, Vgontzas AN (2023) Cretan Aging Cohort-Phase III: methodology and descriptive characteristics of a long-term longitudinal study on predictors of cognitive decline in non-demented elderly from Crete, Greece. *Healthcare (Basel)* **11**, 703.

[4] Fountoulakis KN, Tsolaki M, Chantzi H, Kazis A (2000). Mini mental state examination (MMSE): a validation study in Greece. *Am J Alzheimers Dis Other Dement* **15**, 342–345.

[5] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC (2004) Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* **256**, 240-246.

[6] Basta M, Simos P, Bertsias A, Duijker G, Zaganas I, Koutentaki E, Anastasaki M, Mavroidis G, Kalomoiri G, Panagiotakis S, Lionis C, Vgontzas A (2018) Association between insomnia symptoms and cognitive impairment in the Cretan Aging Cohort. *Eur Geriatr Med* **9**, 697-706.

[7] Skourti E, Simos P, Zampetakis A, Koutentaki E, Zaganas I, Alexopoulou C, Vgontzas A, Basta M (2023) Long-term associations between objective sleep quality

and quantity and verbal memory performance in normal cognition and mild cognitive impairment. *Front Neurosci* **17**, 1265016.

[8] Basta M, Belogianni C, Yannakoulia M, Zaganas I, Panagiotakis S, Simos P, Vgontzas AN (2022) Poor diet, long sleep, and lack of physical activity are associated with inflammation among non-demented community-dwelling elderly. *Healthcare (Basel)* **10**, 143.