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Featured Article

Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study

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Abstract

Introduction: This study tested the hypotheses that late-midlife obstructive sleep apnea (OSA) and short and long sleep duration are associated with dementia for more than 15 years of follow-up.

Methods: A total of 1667 Atherosclerosis Risk in Communities Study participants underwent in-home polysomnography (1996–1998) and were followed for dementia. Dementia was defined by (1) hospitalization diagnosis codes (1996–2012) and (2) a comprehensive neurocognitive examination (2011–2013) with adjudication.

Results: OSA and sleep duration were not associated with risk of incident dementia. When using adjudicated outcomes, severe OSA (≥30 vs. <5 apnea-hypopnea events/hour) was associated with higher risk of all-cause dementia (risk ratio [95% confidence interval], 2.35 [1.06–5.18]) and Alzheimer's disease dementia (1.66 [1.03–2.68]); associations were attenuated with cardiovascular risk factor adjustment. Sleeping <7 versus 8 to ≤9 hours was associated with higher risk of all-cause dementia (2.00 [1.03–3.86]).

Discussion: When adjudicated outcome definitions were used, late-midlife OSA and short sleep duration were associated with all-cause and Alzheimer's disease dementia in later life.

Keywords: Obstructive sleep apnea; Sleep duration; Dementia; Mild cognitive impairment; Alzheimer's disease; Atherosclerosis Risk in Communities (ARIC) Study; Sleep Heart Health Study (SHHS)

1. Background

Dementia and mild cognitive impairment (MCI) pose a major societal burden [1], which is projected to increase because of the aging of the US and global population [2,3]. Effective treatments for dementia and MCI are lacking, thus heightening the need to understand the etiology of these conditions and identify modifiable risk factors. These conditions have a long preclinical phase and for several dementia and MCI risk factors, levels assessed at midlife are more strongly associated with future dementia and MCI risk than are levels assessed later in life (e.g., hypertension [4–6], diabetes [6–10], and smoking [6,11]).

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Evidence from both human and animal studies has suggested a link between obstructive sleep apnea (OSA) and habitual long and short sleep duration with risk of dementia and Alzheimer's disease (AD) [12]. Mechanisms [13,14] hypothesized to underlie these associations include chronic nocturnal hypoxemia [15–17], sleep fragmentation [18], mediation through cardiovascular disease (CVD) risk factors (e.g., hypertension, diabetes, and inflammation), stroke (both clinical and subclinical) [17,19,20], increases in Aβ burden [21], and interaction with the apolipoprotein E (*APOE*) ε4 risk allele [22–26]. However, the relation between sleep and cognitive impairment is incompletely understood; many of the existing epidemiologic studies were limited, in that they did not measure sleep objectively, had a small sample size, and/or were cross-sectional or had short follow-up time, thus raising questions about the temporality of the relationship or reverse causation. In particular, information is lacking about the association between late-midlife sleep characteristics and development of dementia late in life.

Nearly 2000 Atherosclerosis Risk in Communities (ARIC) Study participants had objective sleep measurements at ages 54 to 73 years as part of the Sleep Heart Health Study (SHHS) and were followed to ages 67 to 89 years for neurocognitive outcomes. Using these data, we tested the hypotheses that late-midlife OSA and short and long habitual sleep duration were independently associated with greater risk of developing incident dementia and MCI for more than approximately 15 years of follow-up. Additional analyses were conducted evaluating dementia and MCI of AD etiology.

2. Methods

2.1. Study design

The ARIC cohort includes 15,792 mostly White and Black individuals who in 1987 to 1989 were recruited from four US communities [27]. In 1996 to 1998, which corresponded approximately with ARIC's fourth clinical examination (visit 4), a total of 1920 ARIC participants from the suburbs of Minneapolis, Minnesota, and Washington County, Maryland centers underwent sleep measurements as part of the SHHS [28]. Since study enrollment, ARIC participants have been tracked continuously for hospitalizations and mortality through annual telephone calls (twice-yearly since 2012), surveillance of local hospitals, and monitoring of state and national death indexes. Informed consent was obtained at each clinic visit, and study protocols were approved by relevant Institutional Review Boards.

Of the 1920 ARIC SHHS participants, for the present analysis we excluded individuals with missing data for OSA severity (n = 197), central sleep apnea (n = 28), prevalent dementia at the time of the SHHS examination per dementia hospitalization ICD codes (n = 3), and missing information on key covariates (n = 25). A flow chart is provided in Fig. 1. Of the remaining 1667 participants, all were followed for incident dementia, as defined subsequently, and are included in OSA analyses. The maximal sample size for sleep duration analyses is 1653 because of missing information on habitual sleep duration. Of the 1667 participants, a total of 1083 took part in the ARIC Neurocognitive examination (visit 5, 2011–2013). Only these 1083 individuals were included in the analyses of adjudicated dementia, MCI, and MCI or dementia due to AD. Of participants who did not take part, 359 had died and 225 did not participate for other reasons. Information on these individuals was included in the analyses, as described subsequently.

2.2. Sleep measurements

Unattended polysomnography was conducted in the participant's homes (PS-2 System; Compumedics Limited, Abbotsford, Victoria, Australia), as has been detailed by SHHS Investigators [29]. An apnea was considered present if there was an absence or near absence of airflow (at least <25% of baseline) for ≥10 seconds [28,29]. Hypopnea was defined as a decrease in the amplitude of the airflow <70% of baseline for ≥10 seconds and an oxyhemoglobin desaturation of at least 4%. The apnea-hypopnea index (AHI) was calculated as the number of obstructive apneas (regardless of the oxygen desaturation level) plus hypopneas (with a ≥4% decrease in oxygen saturation) per hour of sleep. Participants were categorized into four OSA severity groups according to the AHI: <5.0 events/hour (normal), 5.0 to 14.9 events/hour (mild sleep apnea), 15 to 29.9 events/hour (moderate sleep apnea), and ≥30.0 events/hour (severe sleep apnea). Percent time with oxygen saturation <90% was also calculated. Central sleep apnea events, which were defined by the absence of airflow with no associated respiratory effort detected, were excluded.

Information about habitual sleep duration during the workdays and weekends was queried through the following questions on the SHHS Sleep Habits Questionnaire: *How much sleep do you usually get at night (or in your main sleep period): on weekdays or workdays* and *on weekends or nonwork days?* Habitual sleep duration per night (hour) was calculated as follows: ([habitual total sleep time during the workdays] × 5 + [habitual total sleep time during the weekends] × 2)/7. Habitual sleep duration was then categorized as <7, 7 to ≤8, 8 to ≤9, and ≥9 hours/night.

2.3. Outcome ascertainment

Ascertainment of dementia and MCI during follow-up was performed through different mechanisms. First, of the 6538 ARIC participants attending visit 5 (2011–2013) (many of whom did not participate in the SHHS), 6471 underwent a detailed neurocognitive assessment, and a selected subset received a neurologic examination and brain magnetic resonance imaging [30]. Second, the modified telephone interview for cognitive status (TICSm), a validated telephone-based cognitive assessment, was performed in