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ORIGINAL ARTICLE

Systemic inflammation as a moderator between sleep and incident dementia

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Abstract

Study Objectives: To determine whether C-reactive protein (CRP), a marker of systemic inflammation, moderates the association between sleep and incident dementia.

Methods: We studied Framingham Heart Study participants who completed at baseline a serum CRP assessment and in-home polysomnography to measure sleep duration, sleep efficiency, sleep latency, wake after sleep onset (WASO), number of awakenings, arousal index, and apnea–hypopnea index. Participants were divided into groups according to their CRP level: low (<1 mg/L), average (1–3 mg/L), and high inflammation (>3 mg/L). Surveillance for outcomes (incident all-cause and Alzheimer's disease [AD] dementia) commenced at baseline and continued up to 22.5 years.

Results: In 291 participants (mean age 67.5 ± 4.9 years, 51.6% men) followed for 13.4 ± 5.4 years, we observed 43 cases of all-cause dementia, 33 of which were clinically consistent with AD. Whereas no direct association between CRP or sleep exposures was observed with incident dementia, CRP levels interacted with nighttime wakefulness when predicting both incident all-cause and AD dementia. In the high CRP group, longer WASO (hazard ratio [HR], 2.89; 95% CI, 1.31–6.34) and more nighttime awakenings (HR, 4.55; 95% CI, 1.19–17.38) were associated with higher risk of incident dementia. In the low CRP group, fewer nighttime awakenings were associated with a higher risk of incident dementia (HR, 0.07; 95% CI, 0.01–0.68).

Conclusions: Our findings suggest that inflammation moderates the association between sleep, particularly nighttime wakefulness, and dementia risk. The presence of inflammation may be an important determinant in evaluating how sleep disturbances relate to neurodegeneration.

Statement of Significance

Although both sleep disturbances and inflammation were reported as risk factors for dementia, it remains unclear how they interact when predicting incident dementia. Because both sleep disturbances and inflammation are treatable, it is important to better understand their contribution to incident dementia. We observed that the association between extended nighttime wakefulness and incident all-cause and Alzheimer's disease dementia was moderated by systemic inflammatory levels. Higher dementia risk was observed with longer and more frequent awakenings in those with high inflammation, but with fewer awakenings in those with low inflammation. These findings suggest that both sleep and inflammatory levels should be considered when identifying individuals at risk for dementia as well as when investigating causal biological pathways for neurodegeneration.

Key words: dementia; Alzheimer's disease; neurodegeneration; epidemiology; mild cognitive impairment; sleep; sleep disorders; sleep quality; C-reactive protein; inflammation

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Introduction

Inadequate sleep has been linked to a number of poor health outcomes [1]. Whereas acute sleep deprivation has long been known to affect cognitive function [2], recent evidence suggests that chronic inadequate sleep is associated with a higher risk of dementia [3]. The relationship is complex since large meta-analyses indicate both self-reported shorter and longer sleep duration are associated with incident dementia [4, 5]. Few studies have used objective sleep assessments with either polysomnography (PSG) or actigraphy, but they reported that various objective markers of disrupted sleep were associated with a higher risk of cognitive impairment [6–11].

Inflammation has also been associated with the incidence of dementia. Inflammatory processes are thought to play a central role in the pathogenesis of Alzheimer's disease (AD) [12]. Higher C-reactive protein (CRP) levels, a marker of systemic inflammation, were associated with a higher risk of incident dementia [13–16]. In specific stages of the neurodegenerative process, however, inflammation may have beneficial effects to combat ongoing pathological events [14, 17–19]. Therefore, although sleep and inflammation have a complex relationship with incident dementia, inadequate sleep combined with inflammation may render the brain more vulnerable to neurodegenerative processes [20, 21].

Sleep and inflammation are also strongly associated: sleep is necessary for an optimal immune response whereas chronic sleep loss may lead to low-grade inflammation [22]. In fact, CRP levels are elevated in association with self-reported and objective measures of poor sleep quality and quantity [23–25]. Recently, it was hypothesized that the presence of inflammation might be a biological pathway exacerbating the impact of poor sleep on neurodegenerative processes [21]. However, the moderating effect of inflammation on the relationship between sleep and incident dementia remains to be explored.

The aim of this preliminary study was to investigate whether serum CRP levels moderate the prospective association between objectively measured sleep with PSG, and incident dementia years later. We hypothesized that inflammatory levels interact with poor sleep quality to affect brain health.

Methods

Sample and overview of the protocol

We studied participants from the Framingham Heart Study Offspring cohort, which started in 1971 [26]. Participants were evaluated approximately every 4 years, for a total of nine examinations. The current study included a subset of participants who completed an overnight PSG as part of the multicenter Sleep Heart Health Study and had CRP levels measured at their 6th examination, between 1995 and 1998 (baseline). Participants were under continuous surveillance for incident mild cognitive impairment (MCI) and dementia from baseline until 2017.

Our sample included persons who were dementia-free at baseline. We excluded those aged <60 years at baseline due to the negligible number of incident dementia cases prior to age 60 in the Offspring cohort. There were 695 participants with PSG at baseline. After excluding participants who were aged less than 60 years at baseline (n = 370), without CRP assessment (n = 7), without follow-up for dementia (n = 5), with prevalent dementia at baseline (n = 2), and persons with inadequate electroencephalogram data for reliable sleep–wake scoring (n = 20), the final sample included 291 participants. All participants gave their written informed consent before the beginning of the study. The Institutional Review Board at Boston University Medical Center's approved the study with human participants.

Exposures: PSG recording and sleep characteristics

The PSG recording was performed in the participants' home and included recording of electroencephalograms, electrooculogram, electrocardiogram, chin electromyogram, oximetry, chest wall and abdomen inductance plethysomnography movements, and nasal/oral airflow (thermistry), ambient light, and position. The portable PSG system was the Compumedics P Series System. Technicians applied the PSG sensors in the evening in the participants' home. Scoring criteria and the PSG protocol were published previously [27–29].

Our primary sleep exposures were measures of sleep quantity and quality: sleep duration, sleep efficiency, and the duration of wake after sleep onset (WASO). In order to further our understanding of how sleep was associated with incident dementia depending on varying levels of inflammation, post hoc secondary sleep exposures were added to examine nighttime wakefulness (sleep latency, number of awakenings per hour of sleep, and arousal index) and the apnea–hypopnea index (AHI), the hallmark of obstructive sleep apnea.

Since the PSG was home-based and unattended by a technician, sleep was not entirely captured for some participants because of displaced sensors, poor contact between the sensor and the participant, technical failures, or environmental contamination. Analyses with sleep duration and efficiency were performed only in participants for whom their sleep was entirely captured (n = 202), and analyses with sleep latency were performed only in participants with adequate lights off data (n = 187). A total of 65 participants had signals that rendered arousals scoring unreliable because of transitory electroencephalogram artifacts (uncertain scoring for more than 10% of arousals), and these participants were excluded for analyses with this variable.

Exposure: blood CRP levels

High-sensitivity CRP levels were measured in serum from a blood draw performed at baseline. Serum was frozen at –80°C until it was thawed in February and March of 2004 for assessment by particle-enhanced immunonephelometry. High-sensitivity CRP in human serum samples frozen at –80°C was previously shown to remain stable for at least 11 years [30]. Dade Behring BN* 100 instrumentation was used with a reagent containing monoclonal antibodies specific to human CRP (Dade Behring High-sensitivity CRP reagent). The measuring range was 0.16–550 mg/L (SI conversion: to convert CRP to nmol/L, multiply by 9.524). Assays were run in singles. Groups were divided by CRP levels into the following categories according to American Heart Association guidelines: low inflammation <1 mg/L, average inflammation 1–3 mg/L, and high inflammation >3 mg/L [31].

Outcome: incident dementia

At every examination, the Folstein Mini-Mental State Examination was administered, and extensive neuropsychological testing was

performed at selected examinations. A participant was flagged for potential cognitive impairment if their Mini-Mental State Examination score dropped below the education-specific cutoff, declined by ≥3 points between two continuous examinations, or declined by ≥5 points compared with their past highest score. Participants were also flagged with suspected cognitive impairment if a physician, staff, family, or the participant themselves raised concerns about their cognition. Annual health status updates and review of hospitalization records were also used to flag suspected cognitive impairment.

Once a participant was flagged with possible cognitive impairment, annual neuropsychological, and neurological evaluations were performed until participants developed dementia or were adjudicated to be normal. Flagged participants were referred to the study's Dementia Review Committee, comprising at least one neurologist and neuropsychologist. MCI was diagnosed according to Petersen criteria [32]. Dementia diagnosis was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV-TR [33]. Dementia due to AD was adjudicated based on the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke, as well as the AD and Related Disorders Association [34].

Statistical analyses

Statistical analyses were performed with SAS software V9.4 (SAS Institute Cary, NC). First, a series of Cox proportional hazards regression models were used to examine the association between sleep exposures or CRP levels at baseline, with incident all-cause dementia and AD dementia up to 22.5 years later. To evaluate the presence of a moderating effect of CRP levels on the association between sleep and dementia, we tested for interactions by CRP groups by including an interaction term in the Cox models. In the presence of significant interactions, associations between the primary and secondary sleep characteristics and incident dementia were stratified by CRP groups with a series of Cox proportional hazards regression models in order to explore the nature of the interaction effect. Cases were censored at the time of their incident event. Nonevents were censored at death or at the date the participant was last known to be dementia-free, through to 2017 corresponding to 22.5 years of follow-up. The proportional hazards assumption was upheld. We confirmed the proportionality of hazards by including time dependent covariates in the Cox model. The time dependent covariates were created as interactions of the predictors and function of survival time, and included in the model. Sleep characteristics were examined as continuous variables in statistical models, and hazard ratios (HR) represent the change in dementia risk by each unit increase in the respective sleep characteristics. Because some variables did not have a normal distribution, data transformations were performed to decrease the effect of potential outliers. A square root transformation was applied to sleep duration and efficiency. A natural log transformation was applied to WASO, sleep latency, the number of awakenings per hour of sleep, the arousal index, and the AHI. In the secondary analyses when CRP was treated as a continuous variable, a natural log was applied. Analyses were adjusted for age and sex. Results were considered significant if $p < 0.05$.

As secondary analyses, we first explored the interaction by CRP levels treated as a continuous variable. We also repeated interactions and Cox models with incident MCI (rather than dementia) as the outcome. For these analyses, persons with prevalent MCI at baseline were excluded, resulting in a sample of 286 participants.

Results

Sample characteristics

The sample included 291 dementia-free participants (mean age: 67.5 ± 4.9 years, 51.6% men) followed on average for 13.4 ± 5.4 years, up to 22.5 years (Table 1). We observed 43 cases of all-cause dementia; 33 were consistent with AD. The average time between baseline and incident dementia in the low CRP group was 9.7 ± 6.0 years, while it was slightly longer in the average (11.9 ± 4.9 years) and high CRP groups (11.8 ± 3.8 years).

Sleep exposures, CRP levels, and risk of dementia

Across the whole sample, we did not observe any significant associations between the sleep exposures or CRP levels (linear CRP, or low and high CRP groups versus average CRP level) and the outcomes of incident all-cause dementia, AD dementia, and MCI (Table 2).

Interaction between CRP levels and primary sleep exposures on the risk of dementia

There was an interaction between WASO and CRP groups on the risk of incident all-cause dementia and incident AD dementia (Table 3). When we stratified results by CRP groups, longer WASO was associated with a higher risk of all-cause dementia and AD dementia in the high CRP group only. When examining CRP as a continuous measure instead of by groups, WASO also significantly interacted with linear CRP to predict incident all-cause dementia ($p = 0.003$) and AD dementia ($p = 0.006$). No interactions were observed for sleep duration or sleep efficiency.

Interaction between CRP levels and secondary sleep exposures on the risk of dementia

To better understand how less consolidated sleep may increase dementia risk, we also analyzed secondary sleep exposures post hoc related to nighttime wakefulness or sleep fragmentation. Sleep by CRP group interactions were observed for the number of awakenings per hour of sleep and the arousal index (Table 3). In the high CRP group, more awakenings were associated with a higher risk of all-cause dementia and AD dementia. Inversely, in the low CRP group, fewer awakenings were associated with a higher risk of all-cause dementia and AD dementia. Trends for a similar effect were observed for the arousal index in the low CRP group, where fewer arousals were associated with a higher risk of all-cause dementia and AD dementia. Interaction results were consistent when examining CRP as a continuous variable instead of CRP groups to predict all-cause dementia (awakenings, $p = 0.004$) and AD dementia (arousal index, $p = 0.034$; awakenings, $p = 0.002$). No interactions were observed for sleep latency or the AHI.

Because of the surprising findings in those with low CRP, we investigated whether these could be attributable to potential

Table 1. Sample characteristics

	Incident dementia sample (*N* = 291)	Incident MCI sample (*N* = 286)
Age (years)	67.5 (4.9)	67.4 (4.9)
Sex (male, *n*, %)	150 (51.6)	146 (51.1)
Education (*n*, %)		
No high school degree	27 (9.3)	25 (8.7)
High school degree	110 (37.8)	109 (38.1)
Some college education	81 (27.8)	81 (28.3)
College graduate	73 (25.1)	71 (24.8)
APOE4 carriers (*n*, %)	67 (23.3)	64 (22.7)
FSRP	0.06 (0.05)	0.06 (0.05)
Body mass index (kg/m^2)*	27.3 (24.8–30.7)	27.3 (24.8–30.7)
Systolic blood pressure (mmHg)	131 (17)	131.5 (17.4)
Treated for hypertension (*n*, %)	105 (36.3)	103 (36.3)
Current smoker (*n*, %)	31 (10.7)	31 (10.8)
Prevalent cardiovascular diseases (*n*, %)	26 (8.9)	25 (8.7)
Diabetes mellitus (*n*, %)	42 (14.4)	41 (14.3)
Total cholesterol (mg/dL)	202.7 (37.9)	203.3 (37.8)
HDL cholesterol (mg/dL)	49.0 (14.4)	49.0 (14.5)
Triglycerides (mg/dL)	139.8 (86.1)	140.3 (86.6)
C-reactive protein*	2.6 (1.0–5.2)	2.7 (1.0–5.2)
Low inflammation <1 mg/L (*n*, %)	72 (24.7)	69 (24.1)
Average inflammation 1–3 mg/L (*n*, %)	87 (29.9)	86 (30.1)
High inflammation >3 mg/L (*n*, %)	132 (45.4)	131 (45.8)
Sleep duration (min)*	365.8 (335.5–399.5)	366.5 (336.0–399.5)
Sleep latency (min)*	16.5 (10–26.0)	17.5 (10–26.5)
Sleep efficiency (%)*	81.7 (74.3–87.3)	82.3 (74.3–87.3)
Wake after sleep onset (min)*	54.5 (33.5–88.0)	53.5 (33.5–87.0)
Number of Awakenings (per hour)*	3.7 (2.7–4.9)	3.6 (2.7–4.9)
Arousal index (per hour)*	18.0 (13.3–24.8)	18.2 (13.5–23.8)
Obstructive apnea–hypopnea index (per hour)*	6.2 (2.3–14.3)	6.4 (2.3–14.3)
Sleeping pills (*n*, %)	41 (14.5)	39 (14.0)
Benzodiazepines (*n*, %)	9 (3.1)	9 (3.2)
Antidepressants (*n*, %)	10 (3.4)	10 (3.5)
Depressive symptoms (*n*, %)	26 (8.9)	26 (9.1)
CES-D ≥16 (*n*, %)	19 (6.8)	19 (7.0)
Incident dementia (*n*, %)	43 (14.8)	-
Incident AD (*n*, %)	33 (11.3)	-
Incident MCI (*n*, %)	-	59 (20.6)

Results are presented as mean (standard deviation) or frequency (percent), except for variables marked with an asterisk that are presented as median (lower quartile–upper quartile) as they were not normally distributed. Follow-up time for dementia was 13.4 ± 5.4 years (min:0.9; max: 22.5). *APOE4*, *apolipoprotein* allele 4 carriers; FSRP, Framingham Stroke Risk Profile; HDL, high-density lipoprotein; CES-D, Center for Epidemiologic Studies Depression Scale; AD, Alzheimer's disease; MCI, Mild cognitive impairment.

ongoing neurodegenerative processes. Therefore, we repeated the analysis censoring the first three years of dementia follow-up, since participants converting to dementia soon after baseline are more likely to have significant neurodegeneration at the time of PSG. When censoring the first three years of follow-up after PSG, two AD dementia cases were removed from analysis that were both in the low CRP group. The result of less awakenings with high AD risk in the low CRP group was still present (int. $p = 0.006$; HR: 0.072, 95% CI: 0.004, 1.21), $p = 0.068$), with a slight change in effect size. However, the finding of less frequent arousals with higher AD risk in the low CRP group was no longer observed (int. $p = 0.072$; HR: 0.34, 95% CI: 0.02, 5.98), $p = 0.457$).

Secondary outcome: incident MCI

Sample characteristics for the incident MCI analysis sample are presented in Table 1. A total of 59 cases (20.6%) of incident MCI were observed over the follow-up period. In the interaction analysis, WASO showed an interaction by CRP groups on the incidence of MCI (Table 4). In the high CRP group, longer WASO was associated with a higher risk of incident MCI. No interactions were observed for any other sleep exposures.

Discussion

In this preliminary prospective community-based study, inflammatory levels moderated the association between nighttime wakefulness and incident dementia. Greater duration of nighttime wakefulness and more frequent awakenings were associated with a higher risk of incident dementia, but only in those with high levels of inflammation at baseline. Surprisingly, in those with low levels of inflammation at baseline, the inverse relation was observed where less frequent nighttime awakenings and arousals were associated with a higher risk of incident dementia. To our knowledge, no study has previously evaluated how sleep and an inflammatory marker interact to predict incident dementia. Our findings suggest that the

Table 2. Sleep variables and CRP levels with risk of incident dementia, AD dementia and MCI

	Incident all-cause dementia			Incident AD dementia			Incident MCI		
Sleep predictors	No. of cases/ sample size	HR (95% CI)	*p*	No. of cases/ sample size	HR (95% CI)	*p*	No. of cases/ sample size	HR (95% CI)	*p*
Primary predictors									
Sleep duration	32/202	1.09 (0.95, 1.25)	0.237	27/202	1.09 (0.93, 1.27)	0.286	43/198	1.08 (0.96, 1.22)	0.192
Sleep efficiency	28/187	1.21 (0.86, 1.71)	0.274	22/187	1.28 (0.87, 1.88)	0.215	36/182	1.24 (0.91, 1.67)	0.169
Wake after sleep onset	43/291	1.35 (0.82, 2.23)	0.239	33/291	1.54 (0.85, 2.79)	0.157	59/286	1.31 (0.85, 2.01)	0.218
Secondary predictors									
Sleep latency	28/184	0.80 (0.52, 1.23)	0.315	22/184	0.80 (0.49, 1.31)	0.380	36/179	0.96 (0.63, 1.47)	0.862
No. of awakenings	43/291	1.34 (0.64, 2.80)	0.433	33/291	1.14 (0.49, 2.63)	0.765	59/286	1.20 (0.63, 2.27)	0.576
Arousal index	35/226	0.73 (0.37, 1.42)	0.356	26/226	0.73 (0.34, 1.57)	0.424	43/222	0.75 (0.40, 1.37)	0.346
Apnea–hypopnea index	40/271	0.99 (0.77, 1.27)	0.945	31/271	1.12 (0.83, 1.50)	0.467	55/266	1.01 (0.82, 1.25)	0.905
CRP levels									
Low CRP*	43/291	1.01 (0.46, 2.24)	0.973	33/291	1.64 (0.64, 4.15)	0.301	59/286	0.96 (0.49, 1.89)	0.903
High CRP*	43/291	0.75 (0.37, 1.52)	0.424	33/291	1.04 (0.44, 2.46)	0.930	59/286	0.76 (0.42, 1.39)	0.376
Linear CRP	43/291	0.88 (0.69, 1.14)	0.339	33/291	0.84 (0.63, 1.12)	0.237	59/286	0.94 (0.76, 1.18)	0.603

Hazards ratios and 95% confidence intervals are presented. Models are adjusted for age and sex. AD; Alzheimer's disease; MCI, Mild cognitive impairment; CRP, C-reactive protein; HR, Hazards ratio.
*Average CRP as a reference.

Table 3. Interaction between sleep and CRP levels on the risk of incident dementia and AD dementia

	Incident all-cause dementia				Incident AD dementia			
Sleep predictors	Int. (*p*)	No. of cases/ sample size	HR (95% CI)	*p*	Int. (*p*)	No. of cases/sample size	HR (95% CI)	*p*
Primary predictors								
Sleep duration	0.688	32/202			0.705	27/202		
Sleep efficiency	0.287	28/187			0.206	22/187		
Wake after sleep onset	0.006	43/291			0.0005	33/291		
Low CRP		11/72	0.52 (0.19, 1.39)	0.191		10/72	0.43 (0.15, 1.25)	0.121
Average CRP		14/87	1.23 (0.52, 2.89)	0.636		8/87	1.06 (0.33, 3.41)	0.919
High CRP		18/132	2.89 (1.31, 6.34)	0.008		15/132	4.36 (1.73, 10.97)	0.002
Secondary predictors								
Sleep latency	0.400	28/184			0.160	22/184		
No. of awakenings	0.005	43/291			0.0008	33/291		
Low CRP		11/72	0.07 (0.008, 0.68)	0.022		10/72	0.07 (0.006, 0.77)	0.030
Average CRP		14/87	1.61 (0.55, 4.74)	0.387		8/87	0.83 (0.20, 3.50)	0.794
High CRP		18/132	4.55 (1.19, 17.38)	0.027		15/132	7.24 (1.50, 34.98)	0.014
Arousal index	0.040	35/226			0.011	26/226		
Low CRP		8/54	0.14 (0.02, 1.05)	0.056		7/54	0.12 (0.01, 1.03)	0.053
Average CRP		13/70	0.58 (0.22, 1.51)	0.263		7/70	0.35 (0.09, 1.31)	0.117
High CRP		14/102	1.51 (0.52, 4.40)	0.455		12/192	1.96 (0.59, 6.50)	0.270
Apnea–hypopnea index	0.290	40/271			0.183	31/271		

All analyses are adjusted for age and sex. CRP levels were used in the interaction factor as categorical. Tests of interaction were considered significant <0.01, and stratified results were considered significant at $p < 0.05$. CRP, C-reactive protein; AD, Alzheimer's disease; HR, hazard ratio.

relationship between sleep and incident dementia differs by levels of inflammation.

Higher dementia risk with greater nighttime wakefulness in the high CRP group

In the high CRP group, we observed that more frequent awakenings and longer WASO were associated with a higher risk of dementia. How greater nighttime wakefulness and elevated inflammatory levels interact to increase the risk of dementia is unclear, but both feature pathological mechanisms that may explain their interaction. Inflammation plays a central role in the pathogenesis of dementia via a large array of cellular signaling pathways, pro-inflammatory dementia risk factors, and facilitation of amyloid-β (Aβ) and tau pathology [12]. In actigraphy studies, greater nighttime wakefulness, including longer WASO and more awakenings, were associated with either cognitive decline or cognitive impairment [6, 35, 36], which may be explained via mechanisms such as impaired synaptic plasticity, formation of atherosclerotic lesions, reduced glymphatic clearance, and increased Aβ deposition [37–41]. Moreover, both disrupted sleep and inflammation are cardiovascular disease risk factors [42], and thus, their combined presence may increase dementia risk via cardiovascular comorbidities [43] Overall, the combined presence of greater nighttime wakefulness and inflammation might have an additive effect on numerous common pathways and increase dementia risk.

Table 4. Interaction between sleep and CRP levels on the risk of incident MCI

	Incident MCI			
Sleep predictors	Interaction (*p*)	No. of cases/sample size	HR (95% CI)	*p*
Primary predictors				
Sleep duration	0.779	43/198		
Sleep efficiency	0.657	36/182		
Wake after sleep onset	0.048	59/286		
Low CRP		15/69	0.80 (0.34, 1.87)	0.609
Average CRP		19/86	0.86 (0.41, 1.81)	0.689
High CRP		25/131	2.36 (1.23, 4.52)	0.0095
Secondary predictors				
Sleep latency	0.116	36/179		
No. of awakenings	0.143	59/286		
Arousal index	0.810	43/222		
Apnea–hypopnea index	0.319	55/266		

Hazards ratios and 95% confidence intervals are presented. Analyses are adjusted for age and sex. CRP levels were used in the interaction factor as categorical. Tests of interaction were considered significant <0.01, and stratified results were considered significant at $p < 0.05$. CRP, C-reactive protein; MCI, mild cognitive impairment; HR, hazards ratio.

In addition, inflammatory levels and greater nighttime wakefulness might affect each other. Greater WASO has been previously associated with a higher inflammatory burden, including elevated CRP levels [25]. In mice, disrupted sleep and prolonged wakefulness resulted in neuroinflammation and impaired hippocampus-dependent learning and memory [44], suggesting that inflammatory processes induced by sleep disruption might be a biological pathway explaining cognitive impairment. On the other hand, a treatment blocking inflammation reduced WASO in those that exhibited high CRP at baseline [45], suggesting that inflammation played a causal role in the disrupted sleep of these patients. However, our findings do not allow to establish a causal association between sleep, inflammation and dementia. Overall, more nighttime wakefulness combined with elevated inflammatory levels might contribute to the pathogenesis of dementia, although how they interact remains to be clarified.

Higher dementia risk with less nighttime wakefulness in the low CRP group

A surprising finding of our study is that, in those with low levels of inflammation at baseline, less frequent nighttime awakenings, and arousals were associated with higher risk of incident dementia. This may be due to ongoing neurodegenerative processes at the time of PSG in those with low CRP levels who later developed dementia. Less nighttime sleep fragmentation might be akin to self-reported long sleep duration, which has been hypothesized to be an early marker of neurodegeneration [5, 46–48]. Because sleep is important for Aβ clearance [40], individuals with certain levels of Aβ burden might compensate with a more consolidated sleep. Moreover, higher Aβ burden was found to be associated with excessive daytime sleepiness, which might represent neurodegeneration of the wakefulness-promoting cerebral centers [49]. New evidence suggests that higher sleep propensity is genetically determined [50], which might also underlie other neurological processes that predispose to neurodegeneration.

It is unclear why a less fragmented sleep is associated with dementia risk only in those with low CRP levels, but this might also be due to ongoing neurodegenerative processes. Although inflammation contributes to dementia pathogenesis, lower levels were observed when there is potentially ongoing neurodegeneration: in older individuals, reduced CRP levels predict the risk of dementia, and CRP levels decreased in the few years before diagnosis [14, 18, 19, 51]. Inflammation might be necessary to "fight off" ongoing neurodegeneration, or those with the highest neuropathology burden might feature reduced inflammation as a compensatory mechanism. In hospitalized patients, longer self-reported sleep duration interacted with higher CRP levels to predict a better global cognitive score [52], suggesting that inflammation in that specific context may be beneficial to cognition. Overall, a less fragmented sleep in those with low inflammatory levels might represent an early marker of ongoing neurodegeneration, and thus, be associated with a higher risk of dementia. However, given that low inflammatory levels and less fragmented sleep are considered healthy, these variables should be evaluated concomitantly with additional predictors of potential neurodegeneration. In the present study, those with low CRP levels who developed dementia progressed to dementia on average two years earlier than those with high CRP levels, suggesting that ongoing neurodegenerative processes might have already been present at baseline. Moreover, the only two participants that converted to dementia in the first three years after PSG were in the low CRP group, leading to an attenuation of the findings we observed with less sleep fragmentation and higher AD risk in the low CRP group. These observations also support that ongoing neurodegeneration contributed to the surprising finding of a more consolidated sleep in those with very low inflammatory levels.

Direct association between sleep parameters and CRP levels with incident dementia

We did not observe any direct association between sleep characteristics or CRP levels and incident all-cause dementia, AD dementia, or incident MCI. While some groups observed an increased risk of AD with higher CRP levels or even with lower CRP, some did not observe any associations [13, 14, 19, 51, 53]. In fact, some groups found similar effects to us, where CRP levels were not directly associated with dementia risk by itself, but was in interaction with another risk factor such as the *APOE4* allele [54, 55]. A few previous studies reported that longer WASO, more

awakenings and other measures of sleep fragmentation were associated with higher risk of cognitive decline and dementia [9, 11, 35, 36], while others observed that WASO and arousals were not associated with the risk of cognitive impairment [7, 56]. However, given the nature of the interactions we observed for these variables, where both more and less sleep fragmentation were associated with increased risk of dementia depending on their inflammatory levels, it is not surprising that direct linear associations were not found. Our results suggest that inconsistencies between studies could partially be due to variability in inflammatory levels across cohorts, and highlight the importance of evaluation the interplay between sleep and inflammation to properly understand their effect on the brain.

While some previous studies have found associations between shorter sleep duration, lower sleep efficiency or longer latency with a higher risk of cognitive impairment, others have not [7, 10, 11, 35, 36, 56]. Additionally, a meta-analysis has found that OSA is associated with an increased risk of cognitive decline and dementia [8]. We did not replicate that finding, which might be because less than a quarter of our sample had OSA (AHI > 15). In fact, because a previous study showed higher dementia risk with severe OSA (AHI > 30) [10], our sample might not have included enough participants with severe OSA to show an effect.

Limitations

Strengths of this study include the careful surveillance for incident dementia, the long follow-up in a population-based sample and the use of gold-standard PSG to objectively investigate sleep characteristics. Limitations of our study included our mostly Caucasian sample, which may reduce the generalizability of our findings. Moreover, there might be a first night effect of the PSG recording, where people sleep worse than they generally do during their first PSG study, although this might be limited by the in-home PSG protocol. Moreover, because of a lack of circadian data, we could not evaluate participants' chronotypes, which could affect how sleep parameters such as latency, duration or efficiency at the time of the PSG are related to incident dementia. The single assessment of both PSG and CRP level may also have limited our ability to measure habitual sleep fragmentation and inflammatory levels. Lastly, in this preliminary study, we had a small number of incident dementia cases when stratifying results by inflammatory levels, although we still observe strong and consistent associations through various nighttime wakefulness measurements and cognitive outcomes. Because we were underpowered, we added secondary sleep exposures post hoc to explore whether WASO interactions were consistent with other sleep fragmentation variables without correcting for multiple comparisons. This preliminary study needs to be replicated in a sample with more dementia cases.

Conclusions

Our findings suggest a complex interplay between sleep, inflammation and incident dementia, where inflammatory levels may determine how sleep and incident dementia are associated. Further clarifying the role of inadequate sleep and inflammation on incident dementia has the potential to contribute to our understanding of neurodegenerative processes, the development of easy screening protocols for individuals at risk in clinical settings using sleep and inflammatory data, and the development of preventive therapies.

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