Title: Low-grade inflammation does not mediate the prospective association between self-reported sleep and cognitive function in older people: 8-year follow up from the English Longitudinal Study of Ageing.

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Abstract

Study objectives: Suboptimal sleep patterns predict poorer performance on cognitive function tests in older adults. This study explored whether inflammation may be one mechanism through which sleep influences future cognition.

Methods: Participants were 4877 men and women from the English Longitudinal Study of Ageing who were followed up for 8 years from wave 4 (2008-09) to wave 8 (2016-17). Sleep was measured via self-report at wave 4, while cognitive function was assessed at every wave with tests of orientation, immediate, delayed recall and verbal fluency. C-reactive protein and fibrinogen were used to measure inflammation.

Results: After full adjustment for confounders, greater sleep problems predicted higher performance on orientation task (β = 0.041, confidence interval (C.I.) 0.001 to 0.080) in women. In men, short sleep predicted lower scores on the delayed recall test (≤6 h: β = -0.334, C.I. -0.601 to

-0.067; >6-7 h: β = -0.254, C.I. -0.496 to -0.012). There was no evidence of mediating effects of inflammatory markers in the relationship between sleep problems, sleep duration and cognitive function tests in both sexes.

Conclusions: Sleep problems and short sleep duration are associated with the subsequent cognitive function in older men and women, but we found no real evidence of any mediating biological effects of inflammatory markers. Given the high prevalence of aberrant sleep and impairments in cognitive performance seen in older adults, more studies are urgently needed to test whether inflammation could be increasing the burden of deleterious sleep on cognition.

Keywords: sleep problems, sleep duration, cognitive function, inflammation, longitudinal, ageing.

1. Introduction

Poor sleep becomes increasingly prevalent with advancing age. For example, up to 50% of elderly individuals struggle with falling asleep [1]. Older people also experience more frequent night awakenings, and spend less time in deep and rapid eye movement (REM) sleep [2]. Disturbed and curtailed sleep, on the other hand, adversely affect numerous aspects of physical and mental health. This is particularly relevant for older adults whose risk of physical and mental diseases and disability increases substantively with advancing age [3].

Amongst its many roles, sleep has been implicated in cognitive performance. For example, experimental studies have shown that sleep deprivation and disturbance of circadian rhythms, which is also frequently reported in ageing adults [1], is associated with diminished cognitive function such as reduced attention, working memory and accuracy [4,5]. However, the evidence relating sleep patterns with cognitive function in population-based studies of older adults is conflicting and prospective cohort studies are still lacking. Briefly, in Whitehall II study middle-aged adults, whose sleep duration either increased or decreased from 7-8 hours at baseline, had lower cognitive performance on a number of cognitive tests [6]. Becoming either a short or longer sleeper was also linked to poorer cognitive performance in older women from the Nurses' Health Study; extremes of sleep duration (≤5 hours or ≥9 hours) at baseline were similarly predictive of worst scores on cognitive tests [7]. A 22.5-year follow-up of the Finnish Twin cohort found that participants with short and long sleep hours also had poorer performance on a range of cognitive batteries [8]. However, a recent prospective analysis of the Doetinchem Cohort Study showed that long but not short sleep hours were predictive of a lower global cognitive function, memory and flexibility [9]. Long [10-12] and short sleep duration [11] have also been found associated with cognitive function cross-sectionally.

Sleep duration does not capture other issues with sleep prevalent in older adults, such as difficulties with falling or staying asleep, yet few studies explored the prospective relationship between sleep disturbances with cognitive function. For example, Virta et al. [8] found that poor sleep quality predicted lower cognitive function scores at a 22.5-year follow-

up. Cross-sectional studies in Denmark, the US, and recently the UK [13-15, respectively] found that disturbances of sleep measured with the Pittsburgh Sleep Quality Index (PSQI) were associated with a reduced performance on a range of cognitive tests. In contrast, [12 and 16] reported no associations between the PSQI and cognitive function. Cross-sectional analysis of the English Longitudinal Study of Ageing (ELSA) revealed that (unexpectedly) greater sleep disturbances were found among participants with the highest scores on cognitive function tests [11].

The few published studies that used objective sleep monitoring have also suggested that sleep is linked to cognitive function. A cross-sectional investigation of the Rotterdam study reported that longer sleep latencies were associated with poorer word recall and fluency [17]. Blackwell et al. [12] found that older men who spent more time awake after initially following asleep and those with longer sleep durations had (modestly) lower scores on cognitive function tests than good sleepers. In the Osteoporotic Fractures in Men Study reduced time spent in REM sleep and extended time spent in stage 1 sleep, which are both frequently found in older people, both predicted worst performance in cognitive function approximately 3.4 years later [18].

Taken together, compared with optimal sleep, short, long and disturbed sleep predict poorer performance on cognitive tests in middle-aged and older adults. Several mechanisms have been proposed as possible mediators of this relationship, and peripheral inflammation is one probable pathway through which sleep can adversely affect cognitive processes [19]. Indeed, older age is associated with greater concentrations of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 [20]. Experimental and population-based studies have shown that individuals with suboptimal sleep patterns have elevated markers of inflammation [21]. There is also some, albeit limited and inconsistent, evidence that raised levels of inflammatory markers predict future cognitive impairment [22]. More recently, prospective analysis of ELSA revealed that CRP and fibrinogen both predicted worst performance on episodic memory tests [23]. However, a different analysis of ELSA found no link between CRP and memory score 10 years later [24]. Very few studies have attempted to

integrate the evidence on sleep, inflammation and future cognitive function. There is some evidence from animal research [25] and clinical populations [26] lending tentative support for the mediating role of inflammatory factors, but a 2-year follow-up of the Singapore-Longitudinal Aging Brain Study found that CRP was unrelated to cognitive performance or sleep [27].

In light of the limitations of the literature discussed above the main aim of this study was to test the hypothesis of whether the association between self-reported sleep measures and cognitive function is mediated by inflammatory factors. Given that sex differences have been reported in the relationships between sleep and inflammation [21], and between sleep and cognitive function [5] all analyses were stratified by sex.

2. Method

2.1 Participants and procedures

This study is based on data from the English Longitudinal Study of Ageing (ELSA) [28], a multi-disciplinary prospective cohort study designed to research the dynamics of ageing. The cohort is nationally representative of men and women aged 50 years and older living in England. The study began in 2002-03 and participants are assessed biannually. In ELSA data are collected in participants' home using a computer-assisted personal interview (CAPI) and a nurse visit a few days later, during which blood (details described below) and other medical information are obtained.

Analyses presented here are based on participants from waves 4 (2008-09), 6 (2012-13) and 8 (2016-17). Wave 4 is used as baseline since this was when sleep measures were introduced to ELSA for the first time. When we tried to restrict our analytical sample to participants who provided sleep, covariate, inflammation (CRP and fibrinogen) and cognitive information measures at baseline, CRP and fibrinogen at wave 6 and cognitive measures at wave 8 this reduced the sample to N=2548. This would have reduced the statistical power and posed a threat of type II error; we would have also been prevented from running sex-stratified analyses. (Differences between participants with complete data on all variables and those with missing data on one or more variable are detailed in the Statistical approach

section). We, therefore, decided to restrict our analytical sample to participants with complete baseline data on all covariates, sleep measures, inflammatory factors and cognitive function variables (N=4877).

Signed consent was obtained from all participants, and ethical approval was issued by the National Research Ethics Service.

2.2 Measures

2.2.1 Socio-demographic measures

All measures described here were obtained during the CAPI. Socio-economic circumstances were estimated by total household wealth taking into account financial wealth (e.g., savings), the value of any property (less mortgage), and the value of any business assets and physical wealth (e.g., artwork), net of debt. Wealth is the most reliable indicator of socio-economic position in ELSA and was divided into quintiles for these analyses. Educational attainment was categorised into 6 categories: "degree level education", "lower than degree education", "GCE (General certificate of education) A-level equivalent education", "up to GCE/O-level education", "foreign or other qualification" and "no formal qualifications".

2.2.2 Sleep measures

Sleep problems were indexed with three questions referring to the most frequent insomnia symptoms, namely: difficulties falling asleep, waking up several times a night and waking up in the morning feeling tired. These sleep items were derived from the Jenkins Sleep Problems Scale [29]. Participants answered these questions with regards to the past month. Items were rated on a 4-point Likert scale (anchored at 1 = "not during the past month" to 4 = "three or more times a week"), and scores were averaged (range 1-4) with higher scores indicating more sleep problems. The Cronbach's alpha at wave 4 for this analytical sample was 0.60.

Sleep duration was measured with an open-ended question asking participants about their sleep duration on an average weeknight. For the analyses described here sleep duration

was categorised into "≤6 h" (short sleep duration), ">6-7 h", and ">7-8 h" (optimal sleep duration). We initially split short sleep hours into "≤5 h" and ">5-6 h", but since only N=594 participants reported sleeping 5 or fewer hour, as to increase statistical power, we combined them with those reporting ">5-6 h"; this gave us N=1527 for the "≤6 h" category. These cut-off points have been used in the literature on this topic [30]. In our analytical sample, we only had N=327 participants who reported long sleep hours (">8 h"). To avoid type II error, we do not report findings for this sleep category. This small number of cases would have also affected the power for our sex-stratified analyses.

2.2.3 Biological data

Blood samples were obtained during the nurse visit. Blood samples were not taken from participants who had clotting disorders or who were taking anti-coagulant medication, and some blood sampled failed to provide sufficient quantities for analysis from older patients. C-reactive protein was analysed using the N Latex C-reactive protein mono immunoassay on the Behring Nephelometer II analyser. Fibrinogen concentrations were quantified using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 analyser [31]. All blood samples were analysed in the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK. For further details relating blood analyses see Craig et al. [31].

2.2.4 Cognitive function measures

Cognitive function was measured at each wave with verbal fluency, immediate and delayed memory recall as well as time orientation.

Verbal fluency was measured with animal naming, a task reflecting executive function. Participants were required to name as many animals as possible within 1 minute. The total number of names represented the measure of verbal fluency, with a higher score representing better executive function.

Verbal memory was measured with a word recall test. A random ten-word list was read by a computer with the speed of one word every two seconds. Participants were required

to remember as many words as they could, immediately and after a short delay. We used the independent measures of immediate and delayed recall (with scores ranging on each task from 0 to 10), with higher scores indicating better immediate and delayed memory.

Time orientation was assessed using questions relating to day and date from the Mini-Mental State Examination [32]. Higher score means superior performance.

2.2.5 Health-related variables

The presence of chronic illness was assessed during the CAPI. Those who responded positively to this question were further requested to report whether their condition limited their activities. Answers were categorised into "yes" for limiting long-standing illness and "no" for its absence. Height and weight were assessed by the nurse and were used to calculate body mass index (BMI, kg/m^2). Data on smoking were collected by asking respondents whether they have ever smoked, and those who responded positively were further asked to state if they still smoked. Responses were classified into "no" for never/past smokers and "yes" for current smokers. Physical activity was indexed by asking whether respondents participated in mild, moderate and vigorous physical activity. For the analyses described here, we categorised responses into "moderate or vigorous physical activity less than once per week" and "moderate or vigorous physical activity at least once per week". Alcohol consumption was measured by asking respondents how many times they had an alcoholic drink in the last 12 months. In this article responses were categorised into "5-6 days a week or daily" and "less than daily".

Depressive symptoms were assessed with an 8-item version of the Centre for Epidemiologic Studies Depression scale (CES-D) initially modified for the Health and Retirement Study in the US [33]. For our analyses, the item concerning sleep was removed from the CES-D as to avoid the issue of shared variance with the measure of sleep problems. The 7-item scale was answered with a "yes" or "no" response. Scores were totalled (range 0-7) and greater scores were reflective of higher depressive symptoms. The Cronbach's alpha for the scale at wave 4 was 0.80.

2.3 Statistical analysis

C-reactive protein data were skewed at waves 4 and 6, and their distribution was normalised prior to analysis. In this article, CRP was treated as a continuously distributed measure. To rule out that participants with CRP ≥10 mg/L had an acute inflammatory response (infection) [34] at the time bloods were collected we excluded them from our analyses.

In comparison with participants who had complete data on all variables used in our analyses (waves 4, 6 and 8, N=2548) those with missing information were older (66.4 vs. 63.8 years, P<0.001), more likely to be in the lowest wealth quintile (20.3% vs. 11.4%, P<0.001), and to have no formal qualifications (31.9 vs.19.3, P<0.001). With regards to health-related variables, participants with missing data were less likely to exercise moderately and vigorously more than once per week (58.3% vs. 74.3%, P<0.001), and they were more likely to currently smoke (15.1% vs. 10.6%, P<0.001). They also had a slightly higher BMI (28.3 vs. 28.0, P=0.005), were more likely to have elevated depressive symptoms (1.17 vs. 0.76, P<0.001), and report a limiting chronic illness (38.7% vs. 25.2%).

All analyses were adjusted for age, wealth, educational attainment, smoking status, alcohol consumption, physical activity, BMI, limiting long-standing illness and depressive symptoms since these are related to sleep and cognitive function measures [35-37]. Our models were also adjusted for baseline CRP, fibrinogen and the corresponding test on cognitive performance.

Mediation analysis was performed using the PROCESS package (version 3) for SPSS [38]. Baseline sleep measure at wave 4 was the exposure factor, an inflammatory variable at wave 6 was the potential mediator, and cognitive function at wave 8 was the outcome variable. In our analyses the total effect (*c*, see Tables 2-5) is the sum of the direct and indirect effect of the sleep measure on cognitive function. The direct effect (*c',* see Tables 2-5) is the effect of the sleep measure on cognitive function after adjustment for an inflammatory factor. Finally, the indirect effect (*ab,* see Tables 2-5) is the effect of our sleep measure on cognitive function through an inflammatory factor [39]. Separate analyses were performed for CRP and

fibrinogen, and sleep problems and duration. Results are presented as unstandardized coefficients and 95% confidence intervals (95% C.I.). For indirect effects, 95% C.I. were calculated using bootstrapping, with 5000 bias-correcting (Bc) bootstrap samples (5000 is a default option in the PROCESS package v.3) [38].

All analyses were performed in SPSS v. 21.

3. Results

3.1 Baseline participants' characteristics

In our sample, men were more likely than women to have a degree and had slightly more wealth. In terms of health-related variables, considerably more men than women drank alcohol daily, but more women reported a limiting long-standing illness and had higher levels of inflammatory markers. Women also reported more sleep and depressive symptoms than men, and more women were short sleepers. However, women scored higher than men in the immediate and delayed recall test as well as in the orientation task (see Table 1).

Table 1. Baseline participants characteristics (N=4877).

Variable	Mean (SD)/N (%)		
	Men (N=2203)	**Women (N=2674)**	***P*-value**
Age	65.4 (8.8)	65.8 (9.3)	0.101
Education attainment			<0.001
Degree	548 (24.9)	396 (14.8)	
Less than a degree	447 (20.3)	341 (12.8)	
GCE A-level/equivalent	203 (9.2)	219 (8.2)	
Up to GCE/O-level	490 (22.2)	676 (25.3)	
Foreign or other qualification	95 (4.3)	271 (10.1)	
No formal qualification	420 (19.1)	771 (28.8)	
Wealth quintiles			0.001
Poorest quintile	273 (12.4)	391 (14.6)	
2nd quintile	366 (16.6)	517 (19.3)	
3rd quantile	447 (20.3)	561 (21.0)	
4th quantile	530 (24.1)	563 (21.1)	
Richest quintile	587 (26.6)	642 (24.0)	
Current smoking status			0.157
No	1949 (88.5)	2330 (87.1)	
Yes	254 (11.5)	344 (12.9)	
Alcohol consumption			<0.001
5-6 days a week or daily	640 (29.1)	467 (17.5)	
Less than daily	1563 (70.9)	2207 (82.5)	
Moderate or vigorous physical activity			<0.001
Less than once per week	582 (26.4)	939 (35.1)	
At least once per week	1621 (73.6)	1735 (64.9)	
BMI (kg/m^2)	28.0 (4.3)	28.0 (5.5)	0.596
Limiting long-standing illness			0.001
Yes	587 (26.6)	829 (31.0)	
No	1616 (73.4)	1845 (69.0)	
Depressive symptoms (CES-D)	0.6 (1.3)	1.1 (1.7)	<0.001
Sleep disturbance	2.1 (0.8)	2.4 (0.9)	<0.001
Sleep duration			<0.001
≤ 6 h	608 (27.6)	919 (34.4)	
>6-7 h	780 (35.4)	834 (31.2)	
>7-8 h	673 (30.5)	736 (27.5)	
>8 h[2]	142 (6.4)	185 (6.9)	
CRP[1]	3.0 (4.5)	3.5 (4.7)	0.001
Fibrinogen	3.3 (0.5)	3.4 (0.5)	<0.001
Fluency	21.8 (6.6)	21.1 (6.4)	<0.001
Immediate recall	5.9 (1.6)	6.1 (1.7)	<0.001
Delayed recall	4.5 (1.9)	4.9 (2.0)	<0.001
Orientation	3.78 (0.5)	3.82 (0.5)	0.006

SD = standard deviation; GCE = General Certificate of Education; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression; CRP = C-recatve protein; [1] untransformed data; [2] data shown for descriptive statistics only.

3.2 Sleep problems, CRP and cognitive function

As shown in Table 2, in women, baseline sleep problems were predictive of higher orientation scores (total effect: β = 0.041, C.I. 0.001 to 0.080) at follow-up, but there was no evidence of the mediating effect of CRP (indirect effect: β = -0.000, Bc C.I. -0.001 to 0.001). Sleep problems were unrelated to fluency, immediate and delayed recall tests. There was no evidence that CRP had any mediating effect in these relationships (see Table 2).

In men, sleep problems were not predictive of any cognitive function test 8 years later, and there was also no evidence of any mediating effect of CRP (see Table 2).

Table 2. Summary of mediation analysis for sleep problems, CRP and cognitive function variables.

Exposure variable (wave 4)	**Mediating variable (wave 6)**	**Outcome variable (wave 8)**	**Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)**			**Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)**		
			Women			**Men**		
Sleep problems	**CRP**	**Cognitive function**	**Indirect effect (ab)***	**Total effect (c)**	**Direct effect (c')**	**Indirect effect (ab)***	**Total effect (c)**	**Direct effect (c')**
		Verbal fluency	-0.002 (0.017, 0.010)	0.344 (-0.043, 0.732)	0.346 (-0.042, 0.733)	0.000 (-0.017, 0.018)	0.357 (-0.119, 0.833)	0.357 (0.119, 0.832)
		Verbal memory Immediate recall	-0.000 (0.004, 0.003)	0.024 (-0.073, 0.122)	0.025 (-0.073, 0.122)	0.000 (-0.004, 0.003)	-0.024 (-0.137, 0.089)	-0.024 (0.137, 0.089)
		Verbal memory Delayed recall	-0.001 (0.006, 0.003)	0.036, (-0.082, 0.153)	0.036, (-0.081, 0.154)	-0.000 (-0.005, 0.004)	0.012 (-0.124, 0.149)	0.012 (0.124, 0.149)
		Orientation	-0.000 (0.001, 0.001)	**0.041 (0.001, 0.080)**	**0.041 (0.001, 0.080)**	-0.000 (-0.004, 0.003)	-0.011 (-0.064, 0.041)	-0.011 (0.064, 0.042)

CRP = C-reactive protein; CI = confidence interval. *For indirect effect bias corrected 95% confidence intervals are reported.

3.3 Sleep problems, fibrinogen and cognitive function

In women, sleep problems did not predict any cognitive function test, and there was no evidence of any mediating effects of fibrinogen (see Table 3).

In men, as already reported with regards to CRP, sleep problems were unrelated to future cognitive function and there was no evidence of any mediating effects of fibrinogen (see Table 3).

Table 3. Summary of mediation analysis for sleep problems, fibrinogen and cognitive function variables.

Exposure variable (wave 4)	**Mediating variable (wave 6)**	**Outcome variable (wave 8)**	**Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)***			**Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)***		
			Women			**Men**		
Sleep problems	**Fibrinogen**	**Cognitive function**	**Indirect effect (ab)**	**Total effect (c)**	**Direct effect (c')**	**Indirect effect (ab)**	**Total effect (c)**	**Direct effect (c')**
		Verbal fluency	0.007 (-0.013, 0.034)	0.355 (-0.024, 0.733)	0.348 (-0.031, 0.727)	0.000 (-0.017, 0.018)	0.343 (-0.130, 0.816)	0.343 (-0.130, 0.817)
		Verbal memory Immediate recall	0.003 (-0.002, 0.010)	0.039 (-0.056, 0.134)	0.036 (-0.059, 0.131)	0.000 (-0.004, 0.004)	-0.066 (-0.177, 0.046)	-0.066 (-0.178, 0.046)
		Verbal memory Delayed recall	0.001 (-0.005, 0.009)	0.054 (-0.061, 0.168)	0.052 (-0.062, 0.167)	0.000 (-0.004, 0.004)	0.010 (-0.126, 0.145)	0.010 (-0.126, 0.145)
		Orientation	-0.001 (-0.003, 0.001)	0.038 (-0.001, 0.076)	0.038 (-0.000, 0.077)	0.000 (-0.003, 0.002)	-0.010 (-0.062, 0.043)	-0.010 (-0.062, 0.043)

CI = confidence interval. *For indirect effect bias corrected 95% confidence intervals are reported.

3.4 Sleep duration, CRP and cognitive function

As shown in Table 4 in women sleep duration was unrelated to future cognitive function, and there was no evidence of any mediating effect of CRP.

In men, however, short sleep duration (≤6 h) was predictive of a lower score on the delayed recall test (total effect: β = -0.303, C.I. -0.571 to -0.034), but this was not mediated by CRP levels (indirect effect: β = -0.000, Bc C.I. -0.010 to 0.009). Sleep duration was unrelated to any other cognitive function test, and CRP had no mediating effect on the relationship between sleep hours and cognitive scores (see Table 4).

3.5 Sleep duration, fibrinogen and cognitive function

In women, there was no evidence that sleep duration was associated with cognitive function 8 years later (see Table 5), and sleep duration did not have any impact on future cognition through fibrinogen as well.

In men, in comparison with optimal sleep duration (>7-8 h), those sleeping ≤6 hours (total effect: β = -0.334, C.I.-0.601 to -0.067) and >6-7 hours (total effect: β = -0.254, C.I. -0.496 to -0.012) had worst performance on the delayed recall test at follow-up. However, fibrinogen concentrations did not mediate these associations (indirect effect for ≤6 h: β = 0.000, Bc C.I. -0.010 to 0.009; indirect effect for >6-7h: β = 0.000, Bc C.I. -0.008 to 0.007, respectively).

Table 4. Summary of mediation analysis for sleep duration, CRP and cognitive function variables.

Exposure variable (wave 4)	Mediating variable (wave 6)	Outcome variable (wave 8)	Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)*			Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)*		
			Women			Men		
Sleep duration categories	CRP	Cognitive function	Indirect effect (ab)	Total effect (c)	Direct effect (c')	Indirect effect (ab)	Total effect (c)	Direct effect (c')
≤6		Verbal fluency	0.004 (-0.020, 0.040)	-0.030 (-0.880, 0.800)	-0.033 (-0.864, 0.797)	0.002 (-0.032, 0.041)	-0.058 (-0.997, 0.882)	-0.060 (-0.999, 0.879)
>6-7			0.006 (-0.021, 0.045)	0.584 (-0.226, 1.395)	0.0575 (-0.236,1.386)	0.002 (-0.031, 0.038)	0.077 (-0.773, 0.927)	0.078 (-0.772,0.927)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Verbal memory Immediate recall	0.001 (-0.006, 0.010)	-0.194 (-0.402, 0.014)	-0.194 (-0.402, 0.014)	0.000 (-0.007, 0.008)	-0.143 (-0.365, 0.080)	-0.142 (-0.365, 0.081)
>6-7			0.001 (-0.007, 0.012)	0.054 (-0.150, 0.257)	0.052 (-0.152, 0.255)	-0.000 (-0.008, 0.008)	-0.072 (-0.274, 0.129)	-0.071 (-0.273, 0.130)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Verbal memory Delayed recall	0.001 (-0.006, 0.013)	-0.002 (-0.253, 0.250)	-0.003 (-0.254, 0.248)	-0.000 (-0.010, 0.009)	**-0.303 (-0.571, -0.034)**	**-0.302 (-0.571, -0.034)**
>6-7			0.002 (-0.006, 0.016)	0.195 (-0.050, 0.441)	0.192 0.054, 0.437)	-0.000 (-0.011, 0.008)	-0.213 (-0.456, 0.029)	-0.213 (-0.456,0.030)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Orientation	0.000 (-0.002, 0.003)	0.069 0.017, 0.154)	0.069 (-0.017, 0.154)	-0.002 (-0.008, 0.004)	-0.063 (-0.167, 0.041)	-0.061 (-0.165, 0.042)
>6-7			0.000 (-0.003, 0.004)	0.054 (-0.030, 0.137)	0.053 (-0.030, 0.136)	-0.002 (-0.008, 0.003)	-0.024 (-0.118, 0.070)	-0.022 (-0.116, 0.072)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference

CRP = C-reactive protein; CI = confidence interval.*For indirect effect bias-corrected 95% confidence intervals are reported.

Table 5. Summary of mediation analysis for sleep duration, fibrinogen and cognitive function variables.

Exposure variable (wave 4)	Mediating variable (wave 6)	Outcome variable (wave 8)	Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)*			Fully Adjusted Mediation Analysis (Coefficient β, 95 % CI)*		
			Women			Men		
Sleep duration categories	Fibrinogen	Cognitive function	Indirect effect (ab)	Total effect (c)	Direct effect (c')	Indirect effect (ab)	Total effect (c)	Direct effect (c')
≤6		Verbal fluency	-0.012 (-0.062,0.023)	-0.057 (-0.870,0.757)	-0.045 (0.859, 0.769)	0.003 (-0.029, 0.042)	-0.128 (-1.065, 0.809)	-0.131 (-1.068, 0.806)
>6-7			-0.004 (-0.039,0.023)	0.541 (-0.258, 1.340)	0.541 (-0.258, 1.340)	-0.000 (-0.034, 0.029)	-0.015 (-0.864, 0.835)	-0.014 (-0.864, 0.836)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6			-0.004 (-0.016,0.005)	-0.182 (-0.386,0.021)	-0.179 (-0.382, 0.024)	0.001 (-0.006, 0.011)	-0.185 (-0.407, 0.036)	-0.186 (-0.408, 0.035)
>6-7			-0.001 (-0.010,0.006)	0.038 (-0.162, 0.238)	0.037 (-0.162, 0.237)	-0.000 (-0.008, 0.007)	-0.080 (-0.281, 0.121)	-0.080 (-0.280, 0.121)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Verbal memory	-0.002 (-0.015,0.009)	0.008 (-0.238, 0.254)	0.010 (-0.236, 0.256)	0.000 (-0.010, 0.009)	**-0.334 (-0.601,-0.067)**	**-0.334 (-0.601, -0.067)**
>6-7			-0.001 (-0.011,0.006)	0.184 (-0.058, 0.425)	0.183 (-0.059,0.424)	0.000 (-0.008, 0.007)	**-0.254 (-0.496,-0.012)**	**-0.254 (-0.496,-0.012)**
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Orientation	0.001 (-0.002,0.005)	0.058 (-0.024, 0.141)	0.058 (-0.025, 0.140)	-0.001 (-0.006, 0.003)	-0.060 (-0.164, 0.044)	-0.059 (-0.163, 0.045)
>6-7			0.000 (-0.002,0.003)	0.033 (-0.048, 0.113)	0.032 (-0.048,0.113)	0.000 (-0.004, 0.005)	-0.001 (-0.095, 0.093)	-0.001 (-0.095, 0.093)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference

CI = confidence interval. *For indirect effect bias-corrected 95% confidence intervals are reported.

4. Discussion

We found that in women, sleep problems were predictive of greater orientation. In men, those reporting short sleep hours at baseline (≤6 h, and >6-7 h) were more likely to have lower scores on verbal memory at follow-up, especially on the delayed recall, when compared with the optimal sleep category (>7-8 h). None of the associations between sleep measures and future cognitive function reported here were mediated by inflammatory factors.

Our finding that more sleep problems at baseline predicted better performance on the orientation corroborates a cross-sectional analysis of ELSA described by Miller at al. [11]. This is, however, in contrast with data described by Virta at al. [8] where disturbed sleep was linked to worst cognitive performance approximately 22 years later. We do not have a strong explanation for this rather counterintuitive finding, and furthermore, this interpretation could be counterfactual. Nonetheless, one possibility could be that participants who perform better on cognitive function tests are also able to record their sleep more accurately. Indeed, the poor cognitive function has been found to influence the level of agreement between self-reported and actigraphy-based sleep data in older adults [40], where those with poorer cognitive function were less accurate in their sleep reports. Lastly, morality represents an important point of attrition in the prospective data linking sleep quality with future cognitive function.

We found that men, but not women in the ≤6 h and >6-7 h sleep categories had lower scores on the delayed recall test 8 years later. This supports the hypothesis that sleep plays an active role in memory consolidation and shows for the first time, to the best of our knowledge, the importance of sleep for delayed memory in older adults. Most previous studies looking at sleep and cognitive function did not look separately at delayed or immediate recall but used an overall memory score, or computed a global cognitive function index from various cognitive tests and domains. Our overall findings are in line with a number of these studies. For example, an earlier cross-sectional analysis of ELSA also found that short sleep was associated with lower scores on cognition, albeit only among those aged 64 or younger [11]. Regarding prospective findings, our study supports data obtained by Virta et al. [8] whereby short sleep predicted lower cognitive scores in men and women aged 65 years on average.

We also corroborate a study described by Lo et al. [27] in which short sleep predicted a decline in cognitive performance of older Chinese men and women. In the Nurses' Health study (composed solely of female participants), short sleep also predicted poor cognitive performance [7]. This is at odds with our data since we only found the relationship in men but not women. Finally, our finding that short sleep predicts lower scores on the delayed recall, when compared with optimal sleep duration, does not support recent prospective analysis of the Doetinchem Cohort Study [9] in which short sleep was unrelated to subsequent cognitive performance.

Sleep fragmentation, hypoxia and disturbed neuronal activity are only a few of the mechanisms through which aberrant sleep might impair cognitive functioning in older adults. Circadian rhythms affect activity in frontal, thalamic, and hypothalamic regions of the brain, impairing learning and memory. Findings from animal studies have supported these potential mechanisms [see 19 for a review on this topic].

In our data, the prospective association between sleep problems and duration with future cognitive function was not mediated by inflammatory factors, namely CRP and fibrinogen. In a study of older Chinese adults CRP was also unrelated to sleep and cognitive function [27], albeit the authors did not perform a mediation analysis, so our findings cannot be directly compared with that data. Greater levels of inflammatory factors have been found associated with reduced cognitive function in patients with obstructive sleep apnoea [26], and in animal studies of acute sleep deprivation [25]. This raises the possibility that more severe sleep disturbances than reported by our participants are needed to raise inflammation, which could then adversely affect cognition. More studies are warranted to explore if inflammation may be translating the deleterious impact of aberrant sleep on future cognition in community-dwelling older adults.

The strengths of our study include a prospective design of (older) adults who are chosen to be representative of men and women living in England. Since a large number of data are collected as part of ELSA, this minimises the risk that participants are aware of researchers' interests such as sleep and cognitive function described here.

Our findings must be interpreted in light of the limitations of our data. Sleep was measured by self-report, which is prone to misperception and bias [41,42]. We also do not have information about sleep disorders such as sleep apnoea and insomnia since these were not collected in wave 4 of ELSA that was our baseline, but all analyses were adjusted for the presence of limiting long-standing illness, smoking, BMI and depressive symptoms, which are relevant for these disorders. Attrition is a well-known issue in longitudinal studies including ELSA, and participants excluded from our analyses were older, more likely to have no formal qualifications; they also reported more depressive symptoms and limiting long-standing illnesses. Albeit we adjusted our data for a number of potential confounders, we cannot rule out the possibility that the same results would have been obtained from those excluded from our analyses. Due to a small number of participants in the long sleep category (8> h) in our analytical sample, we decided to exclude it from our analysis in order to avoid the risk of type II error. This, regrettably, prevents us from comparing our data with previous findings where long sleepers have been found to score lower on cognitive function tests [7-9].

In conclusion, our study adds to the body of evidence that adverse sleep patterns are prospectively associated with performance on cognitive function tests in older men and women. We found that women who were reporting more sleep problems had higher scores on the orientation test than those reporting fewer sleep complaints. In men, in comparison with optimal sleep duration, short sleepers had lower scores on the delayed recall test. However, inflammatory factors did not mediate the prospective association between sleep and cognitive performance reported here. Given the high prevalence of aberrant sleep and reduction of cognitive performance seen in older adults, more studies are urgently needed to test whether inflammation could be increasing the burden of deleterious sleep on cognition.

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