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.

Short title: Sleep and cognition in ageing adults.

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Summary

Suboptimal sleep patterns predict poorer cognitive function in older adults, and induce inflammatory responses. Inflammation could also adversely affect cognitive function. This study explored whether inflammation may be one biological mechanism through which sleep influences follow-up cognitive performance. Participants were 4877 men and women from the English Longitudinal Study of Ageing who were followed-up for 8 years starting at wave 4 (2008-09), through wave 6 (2012-13), and until wave 8 (2016-17). Sleep quality was indexed through self-report enquiring about difficulties falling asleep, waking up several times a night, and waking up in the morning feeling tired. Sleep duration was ascertained by asking about average sleep duration in the weeknight. Cognitive function was assessed with tests of verbal fluency, memory (immediate and delayed recall) and time orientation. After adjustment for confounders, poor sleep quality at baseline predicted higher performance on time orientation at follow-up (β = 0.041, confidence interval (C.I.) 0.001 to 0.080) in women. In men, in comparison with optimal sleep duration, short sleep measured at baseline predicted lower scores in delayed memory recall at follow-up (≤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 measures and cognitive function in both sexes. In conclusion, baseline poor sleep quality and short sleep duration are associated with follow-up cognitive function in older adults, but we found no evidence of any mediating effects of inflammatory markers.

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

Introduction

Poor sleep becomes increasingly prevalent with advancing age (Crowley, 2011), which adversely affects numerous aspects of physical and mental health. For example, too short (typically defined as ≤5–6 h per night), too long (typically defined as >8 h per night) sleep, and sleep of poor quality increase the risk of cardiovascular outcomes and mortality (Cappuccio *et al.,* 2011; Sofi *et al.,* 2014), type 2 diabetes, obesity and hypertension (Jike *et al.,* 2018; Schmid *et al.,* 2015), as well as subsequent depression (Koyanagi *et al.,* 2014; Zhai *et al.,* 2015). This is particularly relevant for older adults, whose risk of physical and mental diseases and disability increases substantively with advancing age (Franco *et al*., 2009).

Growing evidence seems to suggest that unhealthy sleep patterns also have an adverse impact on cognitive function. Briefly, in the Whitehall II study, middle-aged adults, whose sleep duration either increased or decreased from 7-8 hours between baseline and follow-up assessments had lower performance on a number of cognitive tests such as reasoning, phonemic, and semantic fluency approximately 5 years later (Ferrie *et al*., 2011). Becoming either a short or longer sleeper, and extremes of sleep duration (≤5 or ≥9 hours) were also linked to poorer overall cognitive performance in the Nurses' Health Study (Devore et al., *2014*). Similarly, a 22.5-year follow-up of the Finnish Twin cohort revealed that participants with short and long sleep hours had poorer performance on a cognitive test, which was calculated based on cognitive domains such as orientation, short and long term memory and attention (Virta et al., *2013*). However, a recent prospective analysis of the Doetinchem Cohort Study showed that long, but not short, sleep was predictive of a lower global cognitive function, memory and flexibility (van Oostrom *et al*., 2018). Long and short sleep duration have also been found associated with lower cognitive function cross-sectionally (Blackwell *et al*., 2011; Faubel *et al*., 2009; Miller et al., *2014*).

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*. (2013) 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 the UK (Gadie *et al*., 2017; Nebes *et al.,* 2009; Waller *et al.,* 2016) 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, Blackwell *et al*. (2011) and Saint Martin *et al.* (2012) reported no associations between the PSQI and cognitive function. Cross-sectional analysis of the English Longitudinal Study of Ageing (ELSA) revealed that greater sleep disturbances were found among participants with the highest scores on cognitive function tests (Miller *at al*., 2014).

Although the evidence is limited, the few published studies that used objective sleep monitoring have also suggested that sleep is linked to cognitive function. For example, a cross-sectional investigation of the Rotterdam study, which measured sleep with actigraphy, reported that longer sleep latencies were associated with poorer word memory recall and verbal fluency (Luik *et al*., 2015). In the Osteoporotic Fractures in Men Study, which recorded sleep with in-home polysomnography, Blackwell *et al.* (2011) found that older men who spent more time awake after initially following asleep, and those with longer sleep durations, had lower scores on cognitive function tests than good sleepers. A follow-up analysis of these data revealed that reduced time spent in REM sleep, and extended time spent in stage 1 sleep, which are often found in older people, both predicted worse performance in cognitive function approximately 3.4 years later (Song *et al*., 2015).

Experimental studies have also shown that sleep deprivation and disturbance of circadian rhythms, frequently reported in ageing adults, are associated with diminished cognitive function (Franzen *et al*., 2008; Santhi *et al.,* 2016).

Taken together, the current evidence suggests that suboptimal sleep patterns predict poorer performance on cognitive tests in older adults. Several mechanisms have been proposed as possible mediators in this relationship, and there is a growing recognition that inflammation is one probable pathway through which sleep can adversely affect subsequent cognitive processes (Irwin and Vitiello, 2019; Yaffe *et al*., 2014). Firstly, older age is associated with greater concentrations of inflammatory markers, which have been suggested to be a consequence of declining levels of sex hormones, and an increase in visceral adipose

tissue (see Singh and Newman, 2010, for a detailed review). Secondly, a meta-analysis of 72 observational studies comprising of over 50,000 adults reported that individuals with too short and poor sleep quality have elevated markers of inflammation (Irwin *et al*., 2016). Thirdly, there is also some, albeit still limited, evidence that raised levels of inflammatory markers predict follow-up cognitive impairment (Bettcher and Kramer, 2014; Irwin & Vitiello, 2019). Specifically, relative to older adults with low levels of inflammation, those with high levels have been found to have a reduced volume of the hippocampus and medial temporal lobes. Inflammation also exerts a deleterious effect on vascular permeability, endothelial function, and microvascular structure, which subsequently affect white matter (see Bettcher and Kramer, 2014, for a review on this topic). Recently, a prospective analysis of ELSA revealed that higher concentrations of CRP and fibrinogen both predicted worse performance on episodic memory tests (Tampubolon, 2016). However, a different analysis of ELSA found no link between baseline CRP and a follow-up memory score 10 years later (Lassale et al., 2018).

Very few studies to date have attempted to integrate the evidence on sleep, inflammation and follow-up cognitive function. There is some evidence from animal research (Zhu *et al*., 2012) and clinical populations (Haensel *et al*., 2009) lending tentative support for the mediating role of inflammatory factors, but a 2-year follow-up of the Singapore-Longitudinal Aging Brain Study showed that CRP was unrelated to subsequent cognitive performance or sleep (Lo *et al*., 2014). More longitudinal studies are needed to explore the relationship between baseline sleep, inflammation and follow-up cognition.

In light of the limitations of the literature discussed above, the main aim of this study was to test whether inflammatory markers mediate the association between self-reported sleep and follow-up cognitive performance. Based on the available evidence, we hypothesised that the association between baseline sleep and follow-up cognition would be stronger in women than in men, due to the association between sleep measures and inflammatory markers being potentially stronger in women. Specifically, population-based studies have found that women, when compared with men, appear to be more vulnerable to the effects of poor sleep quality and too short sleep duration, and show higher increases in

inflammatory markers such as interleukin-6 and C-reactive protein (Irwin, 2015; Irwin *et al.,* 2016; Irwin and Vitiello, 2019). Previous research has also demonstrated evidence for sex differences in the relationship between sleep and cognitive function, in both young and older adults (De Frias *et al.,* 2006; Santhi *et al*., 2016). Therefore all our analyses were stratified by sex.

Method

Participants and procedures

This article is based on data from the English Longitudinal Study of Ageing (ELSA) (Steptoe *et al*., 2013), which is a nationally representative study of men and women aged 50 years and older living in England. In ELSA data are collected biannually in participants' home using a computer-assisted personal interview (CAPI) and a nurse visit a few days later, during which blood 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 here as the baseline since this was when sleep measures were introduced for the first time. In ELSA, bloods were collected only during the nurse visits that are available at every other wave, and, to date, included waves 2, 4, 6 and 8; therefore, inflammatory markers described in our analyses were selected from waves 4 and 6. Wave 8 was chosen as this is the most recent data available in ELSA. Inflammation, which was considered as a mediating factor in our analysis, was measured at wave 6, an intermediate time point of assessment selected temporally in the middle of the study period between exposure (wave 4) and outcome (wave 8). We selected this temporal order to investigate the deleterious effects of poor sleep quality, or too short sleep, subsequent inflammatory markers measured four years later, on follow-up cognition, measured another four years later.

When we tried to restrict our analytical sample to participants who provided data on sleep, inflammation (CRP and fibrinogen), cognitive function and covariates 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. The 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). However, as part of our sensitivity analyses, we repeated our mediation models on participants with complete data on waves 4,6 and 8, and the results were largely unchanged.

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

Measures

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 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". Age was included as one of our socio-demographic measures as well. These variables were selected for our analysis based on previous research findings indicating their relevance to sleep (Arber *et al.,* 2009; Stranges *et al.,* 2008), cognitive function (Cagney and Lauderdale, 2002), and inflammation (Koster *et al.,* 2006).

Sleep measures

Sleep quality was indexed with three questions from the Jenkins Sleep Problems Scale (Jenkins *et al*., 1988): difficulties falling asleep, waking up several times a night, and waking

up in the morning feeling tired. Participants answered these questions with regards to the past month (anchored at 1 = “not during the past month” to 4 = “three or more times a week”). Scores were averaged (range 1-4) with higher scores indicating poorer sleep quality. The Cronbach’s alpha at wave 4 for this analytical sample was 0.60.

Sleep duration was measured by asking participants about their average sleep duration on a 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. 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 of our sex-stratified analyses.

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. 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 (Craig *et al*., 2006). All blood samples were analysed in the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK.

Cognitive function measures

Cognitive function was measured at wave 8 (2016-17) with verbal fluency, memory as well as orientation, which are the main cognitive measures administered in ELSA at each wave (Steptoe *et al*., 2013).

Verbal fluency was measured with animal naming, a task reflecting executive function. The test measures how quickly participants can think of words from a particular category, counting how many distinct elements from the animal kingdom (real or mythical, excluding repetitions or proper nouns) the respondent can name within one minute. This test requires self-initiated activity, organisation, abstraction and set-shifting abilities (Steel *et al*., 2004). In our study, the total number of correctly named animals represented the measure of verbal fluency, with a higher score representing a superior executive function.

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 (Folstein *et al*., 1975). Higher scores reflect superior performance.

Health-related variables

Participants were requested to indicate whether they had any chronic illnesses or disability. Those who indicated having an illness/disability were further asked whether their condition(s) limited their activities. The response was then stratified into ‘‘yes’’ for limiting long-standing illness, and ‘‘no’’ for the absence of limiting long-standing illness. Information on limiting long-standing conditions was included in our analysis because of the well-established links with sleep (Zee and Turek, 2006), cognitive function (Juster *et al.,* 2010), and inflammation (Singh and Newman, 2010). 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”. The above health-related variables were selected for our analyses because of their well-documented associations with sleep (Stranges *et al*., 2008), cognitive function (Sabia *et al.,* 2008), and inflammation (McDade *et al.,* 2006).

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 (Steffic, 2000). For our analyses, the item concerning sleep was removed from the CES-D, to avoid the issue of shared variance with the measure of sleep quality. 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. We included depressive symptoms in our study since they are closely linked with sleep (Sofi *et al.,* 2014; Koyanagi *et al.,* 2014), cognitive function (Singh-Manoux *et al.,* 2010), and inflammation (Howren *et al.,* 2009).

Statistical analysis

Data were inspected descriptively and graphically. Descriptive statistics were calculated with *t* tests and chi-square tests, as appropriate. All analyses were performed using IBM’s Statistical Package for the Social Sciences (SPSS), version 21.

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. C-reactive protein levels of ≥10 mg/L are indicative of an acute inflammatory response or infection (Pearson et al., 2003), participants above this cut-off point were therefore excluded from analysis.

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 (P<0.001),

more likely to be in the lowest wealth quintile (P<0.001), and to have no formal qualifications (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 (P<0.001), and they were more likely to currently smoke (P<0.001). They also had a slightly higher BMI (P=0.005), were more likely to have elevated depressive symptoms (P<0.001), and report a limiting chronic illness (P<0.001).

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, as described in the Measures section. 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 (Hayes, 2018). 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 (Field, 2018). See Fig. 1 below depicting the conceptual model tested in our study. Separate analyses were performed for CRP and fibrinogen, and sleep quality and duration. All mediation analyses were also repeated in the sample with complete data on all variables used in the study (N=2548). These are reported in the Sensitivity analysis section, while tables are presented as supplementary material. Results are presented as unstandardized coefficients and 95% confidence intervals (95% C.I.). For indirect effects, 95% confidence intervals (C.I.) were calculated using bootstrapping, with 5000 bias-correcting (Bc) bootstrap samples (5000 is a default option in the PROCESS package version 3) (Hayes, 2018). As recommended by Field (2018) and Hayes (2018) we used 95% C.I. (for direct and total effects) and Bc 95% C.I., (for indirect

effects), rather than p-values, to infer whether the observed effects were statistically significant.

Insert Fig.1 around here

Results

Baseline participants' characteristics

Men were more likely than women to have a degree, and had slightly more wealth (see Table 1). In terms of health-related variables, considerably more men than women drank alcohol daily, but more women reported a long-standing limiting, 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 performed better on all cognitive tests included in the study.

Insert Table 1 around here

Sleep quality, CRP and cognitive function

In women, baseline sleep quality was predictive of better time orientation (total effect: $\beta = 0.041$, C.I. 0.001 to 0.080) at follow-up, but there was no evidence of the mediating effect of CRP (indirect effect: $\beta = -0.000$, Bc C.I. -0.001 to 0.001) (see Table 2). Sleep quality was unrelated to verbal fluency, and immediate and delayed recall. There was no evidence that CRP had any mediating effect in these relationships.

In men, sleep quality was not predictive of any cognitive function test 8 years later, and there was also no evidence of any mediating effect of CRP.

Insert Table 2 around here

Sleep quality, fibrinogen and cognitive function

In women, sleep quality 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 quality was unrelated to follow-up cognitive function, and there was no evidence of any mediating effects of fibrinogen.

Insert Table 3 around here

Sleep duration, CRP and cognitive function

As shown in Table, 4 in women sleep duration was unrelated to follow-up 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.

Insert Table 4 around here

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 follow-up 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).

Insert Table 5 around here

Sensitivity analyses

Results from sensitivity analyses broadly confirmed our main findings. In women, baseline sleep quality was predictive of better time orientation at follow-up in models relating CRP (total effect: β = 0.046, C.I. 0.009 to 0.082) and fibrinogen (total effect: β = 0.046, C.I. 0.009 to 0.082), but there was no evidence of mediating effects of either of the inflammatory marker (see Supplementary Table 1 and 2). There was also no prospective association

between sleep quality and other cognitive tests. Baseline sleep duration was unrelated to cognitive scores at follow-up, and there was no evidence of any mediating effects of inflammation.

In men, baseline sleep quality was unrelated to cognition at follow-up, and there was no evidence of any mediation by CRP or fibrinogen. In comparison with the >7-8 h sleep category, men sleeping ≤6 hours had lower scores on the delayed recall test in the model with CRP (total effect: β = -0.315, C.I. -0.584 to -0.045). In the analysis relating fibrinogen men sleeping ≤6 hours (total effect: β = -0.316, C.I. -0.585 to -0.046) and >6-7 hours (total effect: β = -0.175, C.I. -0.419 to -0.070), in comparison with the >7-8 h sleep category, also had poorer performance on the delayed recall test at follow-up. However, there was no evidence of any mediating effects of the inflammatory markers (see Supplementary Table 3 and 4). Baseline sleep duration was unrelated to the other three cognitive tests measured in our study, and there was no evidence of any mediating effects of inflammation.

Discussion

We found that in women baseline sleep quality was predictive of greater time orientation at follow-up. 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 in delayed recall, when compared with the optimal sleep category (>7-8 h). None of the associations between sleep measures and follow-up cognitive function reported here was mediated by inflammatory factors, thus our research hypothesis was unsupported by our data.

Our finding that poorer sleep quality at baseline predicted better performance on time orientation corroborates a cross-sectional analysis of ELSA (Miller *et al*. 2014). This is, however, in contrast with the study by Virta *et al*. (2013) 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. One possibility could be that participants who perform better on cognitive function tests were also able to record their sleep more accurately, given that prior evidence suggested that poor cognitive function has been found to

adversely influence the level of agreement between self-reported and actigraphy-based sleep data in older adults (Van Den Berg *et al*., 2008). However, while a poor cognitive function may impact on how sleep is reported if both measurements are taken at the same time, as was done by Van Den Berg and colleagues (2008), this is unlikely to be the case in our study in which baseline sleep and follow-up cognition were measured 8 years apart.

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 (Kreutzmann *et al.,* 2015), 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. Our overall findings are in line with a number of these studies. For example, an earlier cross-sectional analysis of ELSA found that short sleep was associated with lower scores on cognition, albeit only among those aged 64 or younger (Miller *et al*., 2014). Regarding prospective findings, our study supports data obtained by Virta *et al*. (2013) whereby short sleep predicted lower cognitive scores in men and women aged 65 years on average. We also corroborate a study in which short sleep predicted a decline in cognitive performance of older Chinese men and women (Lo *et al.* (2014). In the Nurses' Health study, composed solely of female participants, short sleep also predicted poor cognitive performance (Devore *et al*., 2014). 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 memory delayed recall test, when compared with optimal sleep duration, does not support recent prospective analysis of the Doetinchem Cohort Study (van Oostrom *et al*., 2018) in which short sleep was unrelated to subsequent cognitive performance.

One possibility why baseline short sleep duration predicted lower performance on the delay memory recall test in men, but not women, at follow-up, could be because we lacked statistical power to also detect this relationship in women. This does not seem to be the case since, in our data, more women than men were short sleepers. However, in our study men

had lower scores on all cognitive tests including the delayed recall memory test. Notably, sex differences in cognition have been reported previously, including in ageing adults (De Frias et al., 2006). Although we adjusted our analysis for baseline cognition and other confounders that could potentially impact follow-up cognition, we cannot rule out the possibility that the association between baseline sleep duration and follow-up cognition was a result of a third unmeasured variable.

A number of experimental studies of sleep deprivation conducted in rodents and humans have documented the importance of sleep duration for effective memory consolidation. Sleep quality also appears to be important, and clinical data from patients with insomnia suggest that poor sleep quality correlates with a diminished sleep-related consolidation of declarative memory (Kreutzmann et al., 2015). Hypoxia and disturbed neuronal activity are also plausible mechanisms through which too short or poor quality 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 (Yaffe *et al*., 2014). Furthermore, as far as memory consolidation is concerned, human neuroimaging studies suggest that the brain region that appears to be particularly sensitive to the consequences of sleep loss or its poor quality is the hippocampus (Kreutzmann *et al.,* 2015).

In our data, the prospective association between sleep quality and duration with follow-up 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 (Lo *et al*., 2014), 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 (Haensel *et al*., 2009), and in animal studies of acute sleep deprivation (Zhu *et al*., 2012). 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 follow-up 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, and estimations of sleep quality (Jackowska *et al.,* 2011) and duration (Lauderdale *et al.,* 2008) are imprecise when compared with sleep data measured objectively. Factors that may influence people's perceptions of sleep include, for example, age, fewer years of education and work stress (Jackowska *et al.,* 2011; Lauderdale *et al.,* 2008). 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. Furthermore, at the time of these analyses ELSA did not have up-to date mortality records. However, sensitivity analyses performed on the sample with complete data on all variables used in the study (N=2548) fully confirmed the findings from our analytical sample (N=4877). 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 (Devore *et al*., 2014; van Oostrom *et al*., 2018; Virta *et al*., 2013).

In conclusion, our study adds to the body of evidence that adverse sleep patterns are prospectively associated with cognitive performance in the elderly. We found that women who were reporting poorer sleep quality performed better on the time 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 memory test. However, inflammatory factors

did not mediate the prospective association between sleep and cognitive performance reported here. Nevertheless, this work opens up possibilities for exploring other mechanistic ways in which a range of modifiable risk factors, such as good sleep, might enhance cognitive functioning in people at older ages, for the possible improvement of health, and social function in the later stages of life.

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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 quality	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
Verbal fluency	21.8 (6.6)	21.1 (6.4)	<0.001
Verbal memory			
Immediate recall	5.9 (1.6)	6.1 (1.7)	<0.001
Delayed recall	4.5 (1.9)	4.9 (2.0)	<0.001
Time 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; CRP = C-recatve protein; [1] untransformed data; [2] data shown for descriptive statistics only.

Table 2. Summary of mediation analysis for sleep quality, 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 quality	**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)
		Time 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. Significant effects are denoted in bold.

Table 3. Summary of mediation analysis for sleep quality, 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 quality	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)
		Time 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. Significant effects are denoted in bold.

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	0.004	-0.030	-0.033	0.002	-0.058	-0.060
		fluency	(-0.020, 0.040)	(-0.880, 0.800)	(-0.864, 0.797)	(-0.032, 0.041)	(-0.997, 0.882)	(-0.999, 0.879)
>6-7			0.006	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
			(-0.021, 0.045)	Reference	Reference	Reference	Reference	(-0.772,0.927)
>7-8			Reference					Reference
≤6		Verbal	0.001	-0.194	-0.194	0.000	-0.143	-0.142
		memory:	(-0.006, 0.010)	(-0.402, 0.014)	(-0.402, 0.014)	(-0.007, 0.008)	(-0.365, 0.080)	(-0.365, 0.081)
>6-7		immediate	0.001	0.054	0.052	-0.000	-0.072	-0.071
		recall	(-0.007, 0.012)	(-0.150, 0.257)	(-0.152, 0.255)	(-0.008, 0.008)	(-0.274, 0.129)	(-0.273, 0.130)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Verbal	0.001	-0.002	-0.003	-0.000	**-0.303**	**-0.302**
		memory:	(-0.006, 0.013)	(-0.253, 0.250)	(-0.254, 0.248)	(-0.010, 0.009)	**(-0.571, -0.034)**	**(-0.571, -0.034)**
>6-7		delayed	0.002	0.195	0.192	-0.000	-0.213	-0.213
		recall	(-0.006, 0.016)	(-0.050, 0.441)	0.054, 0.437)	(-0.011, 0.008)	(-0.456, 0.029)	(-0.456,0.030)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Time	0.000	0.069	0.069	-0.002	-0.063	-0.061
		orientation	(-0.002, 0.003)	(-0.017, 0.154)	(-0.017, 0.154)	(-0.008, 0.004)	(-0.167, 0.041)	(-0.165, 0.042)
>6-7			0.000	0.054	0.053	-0.002	-0.024	-0.022
			(-0.003, 0.004)	(-0.030, 0.137)	(-0.030, 0.136)	(-0.008, 0.003)	(-0.118, 0.070)	(-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. Significant effects are denoted in bold.

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	-0.012	-0.057	-0.045	0.003	-0.128	-0.131
		fluency	(-0.062,0.023)	(-0.870,0.757)	(-0.859, 0.769)	(-0.029, 0.042)	(-1.065, 0.809)	(-1.068, 0.806)
>6-7			-0.004	0.541	0.541	-0.000	-0.015	-0.014
			(-0.039,0.023)	(-0.258, 1.340)	(-0.258, 1.340)	(-0.034, 0.029)	(-0.864, 0.835)	(-0.864, 0.836)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Verbal	-0.004	-0.182	-0.179	0.001	-0.185	-0.186
		memory:	(-0.016,0.005)	(-0.386,0.021)	(-0.382, 0.024)	(-0.006, 0.011)	(-0.407, 0.036)	(-0.408, 0.035)
>6-7		immediate	-0.001	0.038	0.037	-0.000	-0.080	-0.080
		recall	(-0.010,0.006)	(-0.162, 0.238)	(-0.162, 0.237)	(-0.008, 0.007)	(-0.281, 0.121)	(-0.280, 0.121)
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Verbal	-0.002	0.008	0.010	0.000	**-0.334**	**-0.334**
		memory:	(-0.015,0.009)	(-0.238, 0.254)	(-0.236, 0.256)	(-0.010, 0.009)	**(-0.601,-0.067)**	**(-0.601, -0.067)**
>6-7		delayed	-0.001	0.184	0.183	0.000	**-0.254**	**-0.254**
		recall	(-0.011,0.006)	(-0.058, 0.425)	(-0.059,0.424)	(-0.008, 0.007)	**(-0.496,-0.012)**	**(-0.496,-0.012)**
>7-8			Reference	Reference	Reference	Reference	Reference	Reference
≤6		Time	0.001	0.058	0.058	-0.001	-0.060	-0.059
		orientation	(-0.002,0.005)	(-0.024, 0.141)	(-0.025, 0.140)	(-0.006, 0.003)	(-0.164, 0.044)	(-0.163, 0.045)
>6-7			0.000	0.033	0.032	0.000	-0.001	-0.001
			(-0.002,0.003)	(-0.048, 0.113)	(-0.048,0.113)	(-0.004, 0.005)	(-0.095, 0.093)	(-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 Significant effects are denoted in bold.

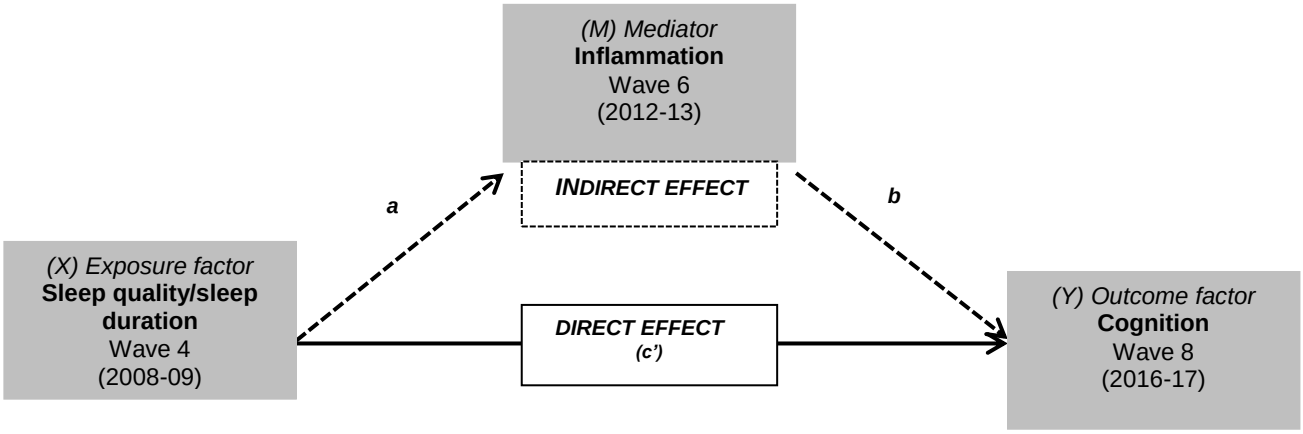

Fig 1. A conceptual figure of the mediation analysis of inflammatory markers (wave 6) between baseline sleep quality/duration (wave 4) and follow-up cognitive functioning (wave 8).