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Sleep and biomarkers in the English Longitudinal Study of Ageing: Associations with C-reactive protein, fibrinogen, dehydroepiandrosterone sulfate and hemoglobin

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Summary Sleep duration and quality are associated with adverse physical health outcomes. The mechanisms are not well understood, and little is known about associations with biomarkers in older population cohorts. This study assessed cross-sectional associations between self-reported sleep measures and biomarkers in a representative sample of British people aged 50 years and above. Participants were 6465 men and women aged 50—99 years from the English Longitudinal Study of Ageing (ELSA). Associations of sleep duration and sleep disturbance with C-reactive protein (CRP), fibrinogen, dehydroepiandrosterone sulfate (DHEAS) and hemoglobin were analyzed, adjusting for age, wealth, body mass index (BMI), smoking, physical activity, limiting long-standing illness and depressive symptoms. In men, long sleep duration (OR: 1.50, 1.05—2.14) and greater sleep disturbance (OR: 1.29, C.I. 1.05—1.59) were associated with raised CRP levels, while long sleep was also related to raised plasma fibrinogen ($P = 0.001$). DHEAS levels were lower among men reporting more sleep disturbances ($P = 0.016$), but were not related to sleep duration. Sleep duration ($P = 0.015$) and sleep disturbance ($P = 0.039$) were associated with lower hemoglobin levels, and anemia was more prevalent among men with disturbed sleep (OR: 1.73, C.I. 1.13—2.65). In women more disturbed sleep was associated with greater likelihood of anemia (OR: 1.59, C.I. 1.02—2.46), but there was no relationship between sleep disturbance or duration with other biomarkers. This study suggests that self-reported sleep duration and disturbance are related to biological risk factors in community-dwelling older adults, with different associations being present in men and women. A better understanding of these relationships using longitudinal cohort studies will broaden our understanding of the mechanisms relating sleep indices and ill health in advancing age.

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1. Introduction

Sleep duration and quality are important for the regulation of physical health. Data from over 1 million men and women in the US revealed that individuals sleeping 7 h on average were least likely to die, while those reporting 8 h or more had significantly higher hazard ratios of mortality (Kripke et al., 2002). More recently short (usually <6 h per night) and long sleep duration (usually >8 or 9 h) as well as sleep disturbance have been implicated in cardiovascular outcomes and mortality (Laugsand et al., 2011; Cappuccio et al., 2011; Hoevenaar-Blom et al., 2011). Sleep parameters are also associated with chronic conditions such as type 2 diabetes and obesity (Stranges et al., 2008). Experimental sleep studies have suggested that inflammatory, immune, autonomic, neuroendocrine and metabolic responses are likely to be involved (Mullington et al., 2009). Such studies usually last only for a few days, so their implications for long-term health risk are uncertain. Large scale population studies provide complementary data concerning biomarkers related to sleep.

The cardiovascular and metabolic problems associated with sleep duration and quality are more common among older people. Sleep duration does not differ markedly between younger and older adults, but sleep efficiency and continuity deteriorate with increasing age (Ancoli-Israel, 2009). Research on biomarkers in elderly cohorts has been limited, and little is known about associations between biological measures and sleep parameters in this population. This may be important for at least two reasons. First, exploring associations between biomarkers and sleep parameters might particularly benefit elderly cohorts, where the accumulation of risk factors increases the risk of mortality and morbidity (Gruenewald et al., 2006). Second, sleep duration and disturbances are amenable to modification, so could provide an opportunity to ameliorate health risk at older ages.

The aim of this study was to assess associations between sleep parameters and biomarkers in a representative sample of British people aged 50 years and older. In the analyses described here we focused on four biomarkers: C-reactive protein (CRP), fibrinogen, dehydroepiandrosterone sulfate (DHEAS) and hemoglobin. CRP is an acute phase protein, which has been shown to predict adverse cardiovascular outcomes and mortality (Libby et al., 2011). Fibrinogen is a marker of inflammation and hemostasis implicated in the development and pathogenesis of cardiovascular disease (CVD) (Danesh et al., 2005). Associations between these inflammatory markers and sleep parameters have been inconsistent (Motivala, 2011). For example, both CRP and fibrinogen have been related to sleep parameters in middle-aged and elderly populations in some studies (Liukkonen et al., 2007; Suarez, 2008; Miller et al., 2009; Matthews et al., 2010; Dowd et al., 2011), but not in others (Miller et al., 2010; Laugsand et al., 2012). Greater variability in sleep-related behaviors, such as later wake up time or longer time in bed, were associated with higher levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in community-dwelling elders (mean age 73.7 years) (Okun et al., 2011). A 30 min sleep restriction over 18 months (to approximately 7 h), however, was not associated with an increase in IL-6 or TNF-α in a sample of healthy adults aged 75 years or older (Reynolds et al., 2010).

ELSA has rich data on biomarkers relevant to health and disease in older age that could shed light on how sleep parameters relate to biological function in elderly populations. Therefore in addition to inflammatory markers we decided to explore associations with dehydroepiandrosterone sulfate (DHEAS) and hemoglobin. Dehydroepiandrosterone (DHEA) and its sulfate form DHEAS are the most prevalent endogenous steroid hormones in elderly populations, though levels decline with age (Labrie et al., 1998). DHEAS has been implicated in cardiovascular health as well and low levels are associated with CVD and all-cause mortality in older men (Barrett-Connor et al., 1986), whereas higher levels are related to better health outcomes such as lower risk of metabolic syndrome (Phillips et al., 2010). However, associations between sleep parameters and steroid hormones are not well understood at present. Hemoglobin is the iron-containing molecule responsible for carrying oxygen from the respiratory organs to the rest of the body, and low levels are usually indicative of anemia. Low levels of hemoglobin and anemia are prevalent in the elderly (Nilsson-Ehle et al., 2000), and anemia is associated with longer hospitalization and greater risk of mortality and CVD (Culleton et al., 2006). As in the case of DHEAS, associations between hemoglobin, anemia and sleep parameters remain largely unexplored in the general or elderly population, but have been studied in children (Peirane et al., 2010).

In this article we describe associations between biomarkers, sleep duration and sleep disturbance assessed with questions related to difficulties falling asleep, saying asleep, and feeling refreshed in the morning. We hypothesized that there might be a curvilinear association with sleep duration, with both short and long sleep duration being related to greater inflammation. We also predicted that greater sleep disturbances would be associated with raised levels of CRP and fibrinogen. Because low levels of both DHEAS and hemoglobin are related to adverse health outcomes we hypothesized that short and long sleep duration as well as greater sleep disturbance would be associated with lower levels of DHEAS, hemoglobin, and greater likelihood of anemia. Since gender differences in associations between sleep parameters and biomarkers have been reported in the literature (Liukkonen et al., 2007; Suarez, 2008; Miller et al., 2009) all analyses were stratified by sex.

2. Method

2.1. Participants and procedures

These analyses are based on data from 6465 men and women aged 50 and older drawn from wave 4 (2008–2009) of the English Longitudinal Study of Ageing (ELSA). ELSA is a prospective cohort study representative of older men and women living in England. The study began in 2002 and participants have been seen biannually since then. Participants in wave 4 included members of the core sample tested in wave 1 (2002), supplemented by refreshment samples in wave 3 (2006/7) and wave 4 (Banks et al., 2010; Steptoe et al., 2012). The response rate in wave 4 was 74%, and the main reason for nonparticipation was refusal (Hussey et al., 2010).

Fieldwork consisted of a computer assisted personal interview (CAPI) and a separate nurse assessment carried out a

few days later. Both were conducted face-to-face in the participants' homes. All participants provided signed consent, and ethical approval was granted by the London Multi-Centre Research Ethics Committee.

2.2. Measures

2.2.1. Demographic variables

Participants' age and gender were assessed during a face-to-face visit in the home. For the purpose of the analyses described here age was re-coded into 4 categories: "50–59","60–69", "70–79" and "80+" years. Socioeconomic status (SES) was indexed by total household wealth, including financial wealth (savings and investments), the value of any home and other property (less mortgage), the value of any business assets and physical wealth such as artwork and jewelry, net of debt. Wealth is the most robust indicator of socioeconomic circumstances in ELSA (Banks et al., 2003) and was divided into age-related quintiles for the purposes of analysis.

2.2.2. Sleep measures

Sleep parameters were assessed during the CAPI. Sleep duration was measured by an open-ended question asking participants to report how many hours they slept on an average weeknight. Responses were coded into "<5 h" (short sleep duration), "5–6 h", "6–7 h", "7–8 h" (optimal sleep duration) and ">8 h" (long sleep duration). Sleep disturbance was assessed with three questions that are the most common symptoms of insomnia. Specifically, participants were requested to indicate whether in the past month they had difficulties falling sleep, staying asleep, and whether they felt tired upon waking up in the morning. These items were rated on a 4-point scale (ranging from 1 = "not during the last month" to 4 = "three or more times a week"). The scores were averaged, with higher scores corresponding to greater sleep disturbances (range 1–4). The Cronbach's α in this sample was .62. Sleep disturbance scores were divided into tertiles prior to analysis. Because women reported more frequent sleep problems than men we computed sex-specific tertiles. In women the 1st tertile (best sleep) ranged from 1 to 1.8, the 2nd (intermediate sleep problems) ranged from 1.81 to 2.8 and the 3rd tertile (poorest sleep) ranged from 2.81 to 4. In men the 1st tertile's range was 1 to 1.8, the 2nd tertile's range was 1.81 to 2.4 and the 3rd tertile ranged from 2.41 to 4.

2.2.3. Biological measures

Participants who had a clotting or bleeding disorder and those on anti-coagulant medication were not asked to provide blood samples. Viable blood samples were obtained from 6188 respondents (75.6% of wave 4 participants) Unless participants were older than 80 years, had diabetes, reported ever having had a fit, were frail or seemed unwell, the nurse collected fasting blood samples, which were defined as not eating or drinking at least 5 h prior to the blood test (4149 respondents provided fasting blood samples) (see de Oliveira et al., 2010 for further details). CRP was measured using the N Latex CRP mono immunoassay on the Behring Nephelometer II analyzer. Fibrinogen was analyzed using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 analyzer. Hemoglobin levels were measured with two Abbott Diagnostics Cell-Dyn 4000 analysers (Craig et al., 2006). DHEAS measures were performed on the DPC Immulite 2000 analyser. All blood samples were analyzed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, UK (see Craig et al., 2006) for a detailed description of blood analyses).

2.2.4. 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. Height and weight, which were assessed by a nurse, were used to calculate body mass index (BMI, kg/m^2). Smoking was assessed by asking participants whether they had ever smoked, and those who stated that they had were further required to indicate whether they still smoked. The responses were then categorized as "yes" for current smoker and "no" for non-smoker. Physical activity was assessed by asking participants how often they engaged in vigorous, moderate or mild physical activity; the response options were "hardly ever or never", "one to three times a month", "once a week" and "more than once a week". In this article physical activity was categorized into engaging in moderate or vigorous physical activity at least once per week or less than once a week.

2.2.5. Other measures

Depressive symptoms were assessed during the CAPI with a shortened version of the Centre for Epidemiologic Studies Depression scale (CES-D) devised for the Health and Retirement Study (Steffick, 2000). In this study we removed the item concerning poor sleep from the CES-D. The scale comprised 7 items that were answered with a "yes" or "no" response. A total score was computed (ranging from 0 to 7), with higher scores corresponding to more depressive symptoms. The Cronbach's α in this sample was .80. Scores were categorized into "no depressive symptoms" (3 or fewer symptoms) and "elevated depressive symptoms" (4 or more symptoms) as described by Steffick (Steffick, 2000).

2.3. Statistical analysis

Fibrinogen ($N = 5928$), hemoglobin ($N = 5995$) and DHEAS ($N = 6028$) were treated as continuous variables in these analyses. Based on a well-recognized cut off of 3 mg/L, CRP ($N = 6061$) was divided into low/normal levels (<3 mg/L) and raised levels (≥3 mg/L) (Pearson et al., 2003). Anemia status (no/yes) was defined based on WHO guidelines (<13 g/dL for men and <12 g/dL for women) (WHO, World health organization, 1968).

Associations between sleep disturbance and biomarkers were tested with logistic regression models for binary variables (anemia, CRP), and with analysis of covariance for continuous measures (fibrinogen, DHEAS and hemoglobin). Hemoglobin and fibrinogen data were normally distributed, but DHEAS data were skewed thus a square root transformation was performed to normalize the distribution. All

analyses were adjusted for age, wealth, BMI, current smoking, physical activity, limiting long-standing illness and depressive symptoms, since these are associated with sleep parameters (Stranges et al., 2008). Curvilinear associations with sleep duration were tested using the 7–8 h category as the reference group. Separate analyses were performed for each biological measure. Analyses were carried out using weighted data, applying a weighting factor relating to non-participation in blood sampling, in order to ensure that survey data matched population estimates in terms of age, sex, housing tenure, ethnicity, educational qualifications, marital status, and region of the country (Hussey et al., 2010). Results are presented as odds ratio (OR) and 95% confidence intervals (C.I.) for logistic regression models, unstandardized regression coefficients (*B*), 95% C.I. and *P*-values for linear regressions, and F-statistics with *P*-values for analysis of covariance. All analyses were conducted using SPSS version 18.

3. Results

Participants' characteristics stratified by gender are depicted in Table 1. 2916 men and 3549 women provided data on at least one biomarker. There were more women than men in the sample. Men tended to have greater wealth, and were more likely to engage in moderate or vigorous physical activity at least once a week. More women reported limiting long-standing illness and had elevated depressive symptoms (12.7% and 6.2%, respectively). As shown in Table 1 there were significant differences in sleep duration and disturbance regarding gender as well ($P < 0.001$, $P < 0.001$,

Table 1 Characteristics of study participants.

Variable	Mean (SD)/frequency (%)		*P* value
	Men (*N* = 2916)	Women (*N* = 3549)	
Age			0.019
50–59 years	874 (30.0)	1101 (31.0)	
60–69 years	1137 (39.0)	1308 (36.9)	
70–79 years	686 (23.5)	805 (22.7)	
80+ years	219 (7.5)	335 (9.4)	
Wealth quintiles			0.001
Poorest quintile	485 (16.6)	687 (19.4)	
2nd quintile	500 (17.1)	693 (19.5)	
3rd quintile	565 (19.4)	679 (19.1)	
4th quintile	610 (20.9)	676 (19.0)	
Richest quintile	626 (21.5)	671 (18.9)	
Current smoking status			0.517
No	2524 (86.6)	3047 (85.9)	
Yes	375 (12.9)	475 (13.4)	
Moderate or vigorous physical activity			<0.001
Less than once per week	850 (29.1)	1306 (36.8)	
At least once per week	2066 (70.9)	2242 (63.3)	
Limiting long-standing illness			0.001
No	2085 (71.5)	2401 (67.7)	
Yes	831 (28.5)	1147 (32.3)	
Depressive symptoms			<0.001
No	2715 (93.1)	3074 (86.6)	
Yes	180 (6.2)	451 (12.7)	
BMI	27.99 (4.33)	28.06 (5.55)	0.537
Sleep duration			<0.001
<5 h	300 (10.3)	520 (14.7)	
5–6 h	538 (18.4)	720 (20.3)	
6–7 h	1013 (34.7)	1059 (29.8)	
7–8 h	872 (29.9)	958 (27.8)	
>8 h	192 (6.6)	252 (7.1)	
Sleep disturbance			<0.001
Low sleep disturbance	1131 (38.8)	951 (26.8)	
Intermediate sleep disturbance	965 (33.1)	1383 (39.0)	
High sleep disturbance	819 (28.1)	1215 (34.2)	

SD = standard deviation; BMI = body mass index.

respectively). More women than men reported short sleep duration (14.7% and 10.3%, respectively) and disturbed sleep (34.2% and 28.1%, respectively).

Sleep duration was positively related to age ($P < 0.001$) and wealth ($P < 0.001$), with older and wealthier individuals reporting longer sleep hours. Sleep duration was shorter among participants with limiting long-standing illness ($P < 0.001$), smokers ($P < 0.001$), those with elevated depressive symptoms ($P < 0.001$) and higher BMI ($P < 0.001$). Individuals who reported short and long sleep duration were less likely to engaged in moderate or vigorous physical activity more than once a week than those who slept 7–8 h ($P < 0.001$). Sleep disturbance was unrelated to age, but was more prevalent in the lower wealth quintiles ($P < 0.001$), current smokers ($P < 0.001$), respondents with limiting long-standing illness ($P < 0.001$), those who had higher BMI ($P < 0.001$), as well as among respondents who took part in moderate or vigorous physical activity less than once a week ($P < 0.001$). Respondents with elevated depressive symptoms also had more disturbed sleep ($P < 0.001$).

BMI was weakly associated with inflammatory biomarkers in these data (CRP ($r = 0.22$, $P < 0.001$), fibrinogen ($r = 0.17$, $P < 0.001$)).

3.1. Sleep duration and biological data

Among men, sleep of longer than 8 h was associated with raised CRP levels compared with those sleeping 7–8 h (OR: 1.50, C.I. 1.05–2.14) (see Table 2). There were no differences in CRP between the shorter sleep periods. Because some past studies relating sleep parameters and inflammation (e.g., Miller et al., 2009; Dowd et al., 2011) analyzed CRP as a continuous variable we repeated the model treating CRP as continuous data. Sleep duration was no longer associated with CRP (in both sexes), but in men the association was in the same direction, with highest levels among men

Table 2 Associations between sleep duration and biomarkers in men and women.

	Percent/adjusted means (SD)[a]	Adjusted odds ratio[a] (95% C.I.)/*P* value for continuous data	Percent/adjusted means (SD)[a]	Adjusted odds ratio[a] (95% C.I.)/*P* value for continuous data
	Men		Women	
C-reactive protein (≥3 mg/L)				
<5 h	28.4%	0.87 (0.64–1.18)	37.9%	0.16 (0.90–1.49)
5–6 h	33.2%	1.18 (0.92–1.51)	35.5%	1.07 (0.84–1.35)
6–7 h	31.3%	1.07 (0.86–1.34)	35.5%	1.05 (0.85–1.31)
7–8 h	31.1%	reference	35.0%	reference
>8 h	37.9%	1.50 (1.05–2.14)	37.7%	1.17 (0.84–1.63)
Plasma fibrinogen (g/L)				
<5 h	3.23 (0.59)	0.001	3.42 (0.56)	0.805
5–6 h	3.34 (0.55)		3.44 (0.56)	
6–7 h	3.30 (0.57)		3.41 (0.54)	
7–8 h	3.34 (0.58)		3.41 (0.54)	
>8 h	3.44 (0.60)		3.43 (0.57)	
DHEAS (μmol/L)				
<5 h	1.66 (0.56)	0.980	1.26 (0.43)	0.054
5–6 h	1.66 (0.55)		1.30 (0.44)	
6–7 h	1.66 (0.54)		1.33 (0.45)	
7–8 h	1.66 (0.55)		1.30 (0.45)	
>8 h	1.68 (0.61)		1.32 (0.49)	
Plasma hemoglobin (g/dL)				
<5 h	14.71 (1.37)	0.015	13.49 (1.13)	0.351
5–6 h	14.68 (1.20)		13.52 (1.11)	
6–7 h	14.79 (1.21)		13.60 (1.00)	
7–8 h	14.80 (1.19)		13.58 (1.05)	
>8 h	14.87 (1.40)		13.43 (1.17)	
Anemia (below hemoglobin threshold)				
<5 h	5.7%	0.97 (0.56–1.69)	5.7%	0.97 (0.61–1.55)
5–6 h	7.2%	1.40 (0.87–2.24)	6.4%	0.98 (0.63–1.52)
6–7 h	5.8%	1.05 (0.67–1.64)	4.6%	0.64 (0.40–1.03)
7–8 h	5.6%	1 (reference)	6.1%	1 (reference)
>8 h	5.3%	1.01 (0.53–1.94)	10.0%	1.54 (0.91–2.62)

[a] Adjusted for age, wealth, BMI, smoking status, moderate or vigorous activity at least once per week, limiting longstanding illness and depressive symptoms.

Table 3 Associations between sleep disturbance tertiles and biomarkers in men and women.

	Percent/adjusted means (SD)[a]	Adjusted odds ratio[a] (95% C.I.)/*P* value for continuous data	Percent/adjusted means (SD)[a]	Adjusted odds ratio[a] (95% C.I.)/*P* value for continuous data
	Men		Women	
C-reactive protein (≥3 mg/L)				
Low sleep disturbance	30.9%	1 (reference)	34.8%	1 (reference)
Intermediate sleep disturbance	34.6%	1.29 (1.05—1.59)	36.5%	1.08 (0.88—1.33)
High sleep disturbance	29.5%	0.97 (0.78— 1.21)	36.6%	1.07 (0.86—1.33)
Plasma fibrinogen (g/L)				
Low sleep disturbance	3.32 (0.56)	0.083	3.42 (0.54)	0.883
Intermediate sleep disturbance	3.35 (0.59)		3.43 (0.54)	
High sleep disturbance	3.29 (0.58)		3.41 (0.57)	
DHEAS (μmol/L)				
Low sleep disturbance	1.69 (0.55)	0.016	1.33 (0.45)	0.146
Intermediate sleep disturbance	1.67 (0.54)		1.30 (0.43)	
High sleep disturbance	1.62 (0.56)		1.29 (0.46)	
Plasma hemoglobin (g/dL)				
Low sleep disturbance	14.84 (1.10)	0.039	13.58 (1.01)	0.499
Intermediate sleep disturbance	14.73 (1.31)		13.55 (1.09)	
High sleep disturbance	14.71 (1.30)		13.52 (1.10)	
Anemia (below hemoglobin threshold)				
Low sleep disturbance	4.7%	1 (reference)	4.5%	1 (reference)
Intermediate sleep disturbance	7.2%	1.73 (1.13—2.65)	6.6%	1.59 (1.02—2.46)
High sleep disturbance	6.3%	1.49 (0.95—2.35)	6.2%	1.49 (0.95—2.33)

[a] Adjusted for age, wealth, BMI, smoking status, moderate or vigorous activity at least once per week, limiting longstanding illness and depressive symptoms.

sleeping longest hours. Sleep duration was also related to fibrinogen ($F(4,2845) = 5.007$, $P = 0.001$), with fibrinogen being higher among long sleepers. There was no relationship between sleep duration and DHEAS concentration, but hemoglobin levels were lower in shorter sleepers independently of covariates ($B = 0.052$, C.I. 0.01—0.09, $P = 0.015$). There was no association between anemia and sleep duration in men. Sleep duration was unrelated to any of the biomarkers among women.

3.2. Sleep disturbance and biological data

Men reporting intermediate levels of disturbed sleep had elevated CRP levels (OR: 1.29, C.I. 1.05—1.59), and the same relationship was found when CRP was treated as a continuous variable ($F(2,2912) = 7.420$, $P = 0.001$). There was no association between sleep duration and fibrinogen (see Table 3). Men with more disturbed sleep had lower levels of DHEAS ($F(2,2899) = 4.126$, $P = 0.016$, and disturbed sleep was also linked with low hemoglobin ($F(2,2882) = 3.239$, $P = 0.039$) and greater likelihood of anemia (OR: 1.73, C.I. 1.13—2.65), independently of age, wealth, BMI, smoking, limiting long-standing illness, physical activity and depressive symptoms.

In women more disturbed sleep was associated with greater likelihood of anemia (OR: 1.59 (1.02—2.46), but there was no relationship between sleep disturbances and the remaining biomarkers.

4. Discussion

This study found gender differences in the associations between sleep measures and biological data, since with the exception of the relationship between disturbed sleep and anemia the effects were present only in men. The hypothesis that there might be a curvilinear association between sleep duration and markers of inflammation was partly supported. Men sleeping long hours had elevated CRP and fibrinogen levels compared with the 7—8 h category. There was a limited support for the hypothesis that disturbed sleep would be associated with raised levels of inflammatory markers since although the association between sleep disturbance and CRP was significant, there was no relationship with fibrinogen. We found that poor sleep is related to lower DHEAS levels, though only in men, but there was no relationship between sleep duration and DHEAS. Short and disturbed sleep was also associated with low hemoglobin concentrations, and disturbed sleep was related to increased risk of anemia as well, independently of covariates.

The findings relating to inflammation are partly consistent with previous studies (Motivala, 2011). The observation that long (>8 h) sleep duration was related to elevated levels of CRP has also been reported in a study of middle-aged and elderly Taiwanese men and women (Dowd et al., 2011). However, other population-based studies of men and women (Suarez, 2008) as well as of middle-aged women (Matthews et al., 2010) failed to find an association between

self-reported sleep duration and this inflammatory marker. In the Whitehall II study CRP was higher in women sleeping fewer than 5 h, but not among those sleeping more than 9 h, and unlike in our study no association was found in men (Miller et al., 2009). The association with sleep duration was only significant when CRP was treated as a dichotomous variable, and not as a continuously distributed measure. This suggests that the relationship is not a graded one, but is only apparent when potentially clinically significant levels of systemic inflammation are present.

Fibrinogen was unrelated to sleep duration in previous studies (Suarez, 2008; Matthews et al., 2010; Miller et al., 2010), but our data suggest that in men long sleep hours are related to higher levels. Sampling differences between our study and those of Suarez (2008) and Matthews et al. (2010) could be one explanation for the lack of this association in their data since the former study was not based on an older population, while the latter comprised only women. The Whitehall II study (Miller et al., 2010) compared men and women but the mean age was approximately 49 years, while our participants were 65 years on average. However our finding supports data from middle-aged and elderly Taiwanese adults where sleep longer than 8 h, but not short sleep, was related to higher fibrinogen concentrations. The mean age in that study was 66 years (Dowd et al., 2011).

Mechanisms relating long sleep duration with health outcomes are not well understood at present (Stranges et al., 2008), but pathways linking short and long sleep hours with health are likely to be distinct. For example, findings from the Whitehall II cohort study revealed that while a reduction in sleep duration predicted cardiovascular mortality, an increase in the hours slept did not (Ferrie et al., 2007). It has been argued that long sleep hours are secondary to pre-existing illness, whereas short sleep precedes ill-health (Stranges et al., 2008). If this is the case, then perhaps greater inflammation is an indicator of pre-existing illness. We did not include specific measures of coronary heart disease, diabetes, or cancer in these analyses, although the presence of a limiting long-standing illness was taken into account. Sleep apnea might be another pathway translating long sleep duration into adverse health outcomes (Foley, 2004). Sleep apnea was not measured in ELSA, but all analyses were adjusted for BMI, age, and smoking which are well-established risk factors for this sleep disorder (Punjabi, 2008; Kasai et al., 2012). Sleep apnea has also been found more prevalent among ethnic minority groups (Sutherland et al., 2012), in particular in Asian and black populations, but our data comprise largely white participants (96.3%). Family history is another risk factor (Kasai et al., 2012), but we do not have information on this variable. Polycystic ovary syndrome and pregnancy are risk factors for sleep apnea in women (Punjabi, 2008). Women in our study were aged 50 years or more and none were pregnant, and analyses were adjusted for limiting long standing illnesses that would have taken into account the presence of polycystic ovaries. The association between long sleep duration and mortality has been correlated with depression and lower SES in previous studies (Patel et al., 2006), but in the present study effects were independent of depressive symptoms and socio-economic circumstances as defined by participants' wealth.

Our data support the association between elevated CRP levels and disturbed sleep (Suarez, 2008; Matthews et al., 2010), but the association was modest and was found only in men. This is in line with the findings from the Northern Finland 1966 Birth Cohort (Liukkonen et al., 2007), as well as with the data from the HUNT study in Norway (Laugsand et al., 2012). Although sleep disturbances have been related to elevated fibrinogen among women (Suarez, 2008; Matthews et al., 2010), our analyses support this association only in men. It is uncertain why our study do not support data previously reported in women, but as already noted in relation to the association between long sleep and fibrinogen, differences in the populations studied may in part explain these divergent findings. In addition to the issues of age and gender discussed earlier, Matthews et al. (2010) found associations between measures of sleep disturbance and fibrinogen only among African American women, and the study described by Suarez (2008) was also based on a multiethnic sample. ELSA comprises of largely white participants (96.3%).

Higher levels of DHEAS have been associated with advantageous health outcomes such as lower prevalence of metabolic syndrome in men (Phillips et al., 2010). To date there has been few studies relating sleep parameters with DHEAS, but an Austrian study of middle-aged and elderly men failed to find an association between sleep quality and DHEAS (Ponholzer et al., 2005), and DHEAS was also unrelated to sleep duration in a sample of Chinese men (aged 29—72 years) (Goh et al., 2007). In our study we found an inverse relationship between sleep disturbance and DHEAS in men, independently of confounders. It has been reported that men tend to have higher DHEAS levels than women (Vermeulen, 1995), and this was also the case in these data ($P < 0.001$). That could explain in part gender differences in the relationship between sleep disturbance and DHEAS in this study. This novel finding suggests that fewer sleep complaints are associated the higher DHEAS among older people. Since DHEAS concentration declines markedly with age, this might be a mechanism through which better sleep promotes health at older ages. Future studies are needed to test the temporal relationship between sleep quality and DHEAS.

Low hemoglobin and anemia are serious issues in elderly populations and have been implicated in adverse health outcomes and mortality (Culleton et al., 2006). Little is known about associations between sleep parameters and hemoglobin levels in elderly community-dwelling individuals. Our data indicate that in men, greater sleep problems and short sleep hours are associated with lower hemoglobin levels, independently of covariates including depressive symptoms. More sleep problems were also related to higher odds of having anemia in both sexes. Given that approximately 34% of anemias in the elderly have unexplained causes (Guralnik et al., 2005) this is potentially an important finding; it suggests that, in addition to nutritional deficiencies or chronic illnesses, behavioral factors such as poor sleep might be implicated in this condition. Short sleep duration was marginally related to lower hemoglobin levels as well (but not to higher odds of anemia). However, because these data are cross-sectional, it is uncertain whether disturbed and short sleep are risk factors or consequences of lower hemoglobin levels and anemia in this elderly cohort. Anemia is related to fatigue (Beghe et al., 2004), which has also been associated with poor sleep (Thomas et al., 2011), so it is

possible that fatigue in part drove the associations between sleep parameters and hemoglobin levels in this study. There is evidence that iron deficiency, which might cause low hemoglobin and anemia, leads to disturbed sleep. For instance, iron deficiency and anemia have been associated with alterations of sleep architecture in pediatric populations (both cross-sectionally and prospectively) (Peirane et al., 2010). Iron deficiency is associated with restless leg syndrome as well, which ranges between 5 and 15% in the general population (Trotti et al., 2012). We do not have information about sleep disorders in ELSA, but all analyses were adjusted for a limiting long-standing illness. Longitudinal studies are required to explore these associations further.

Longer sleep duration was more prevalent with increasing age in these data. It has been well documented that sleep efficiency and continuity diminish markedly as people age, with men showing more pronounced changes than women (Carskadon and Dement, 2005; Ohayon et al., 2004). This does not always seem to be the case with sleep duration. A meta-analytic review of sleep parameters across the lifespan showed that while in healthy adults sleep duration is negatively associated with age, the trend is no longer significant among individuals over 60 years old (Ohayon et al., 2004). More recently data from over 1000 men and women aged 60 years and above revealed that the average sleep duration was 7 h 8 min (Ohayon and Vecchierini, 2005), which does not markedly differ from sleep duration reported by middle-aged individuals (Magee et al., 2009). Older age has been associated with longer sleep duration in a large US study as well (Krueger and Friedman, 2009).

This study has several strengths. These analyses are based on a large and well-characterized sample of older individuals living in England. We were able to take advantage of the extensive economic and health data available in ELSA, and to study a range of biomarkers. Because the variables studied were collected within a larger study protocol, there is little chance that participants were aware of the specific interests of the investigators in sleep and biological function.

These data also have several limitations. Sleep duration and disturbance were assessed with self-reported measures, and these may be affected by memory biases and affective states (Krystal and Edinger, 2008). We used a short scale based on the Jenkins Sleep Problems Scale (Jenkins et al., 1988) rather than a more elaborate measure such as the Pittsburgh Sleep Quality Index (Buysse et al., 1989). However, the items overlap with those included in longer measures, and the Jenkins Sleep Problems Scale has previously been used to investigate outcomes such as sickness absence, weight gain, and recovery from surgery (Jenkins et al., 1994; Lyytikäinen et al., 2011; Lallukka et al., 2012) as well as cardiovascular and neuroendocrine function (Kumari et al., 2009; Jackowska et al., 2012). The use of self-report is common in large community-based research studies, where the expense of using objective sleep measures may be prohibitive, but it cannot be concluded that the associations observed would necessarily be replicated with objective indicators. The cross-sectional design did not permit to establish the temporal precedence between sleep parameters and biological measures in this study. Deviant sleep patterns might lead to poor health, for example through inflammatory responses, but poor health impairs sleep as well (Zee and Turek, 2006). Therefore it should be recognized that the biological measures described in this article could mediate the relationship between poor sleep and ill health, but also be risk factors for disordered sleep. Sleep measures were introduced to ELSA in wave 4, thus it is not yet possible to study longitudinal associations between sleep parameters and biological measures. CRP and fibrinogen are acute phase proteins that may be stimulated by a number of different processes including inflammatory cytokine release from a variety of tissues. It would have been informative to explore relationships between sleep and IL-6 and other inflammatory markers, but these were not measured in ELSA.

In conclusion, disturbed sleep was associated with higher odds of anemia in women, but there was no relationship between sleep measures and other biomarkers. Our findings in male respondents support the growing body of evidence that low grade inflammation, as indicated by CRP and fibrinogen, is associated with long sleep duration. Further we observed for the first time, to the best of our knowledge, an association of DHEAS with sleep disturbance. We have also extended findings relating low hemoglobin and anemia with sleep parameters to a representative sample of older adults. These results support the hypothesis that sleep is an important marker of physical health in the elderly. A better understanding of these relationships, preferably using longitudinal cohort studies, will broaden our understanding of risk factors for ill health in elderly populations.

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Conflict of interest

There are no conflicts of interests.

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