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Associations between dehydroepiandrosterone sulphate (DHEAS) and cognitive function in 5,061 older men and women in the English Longitudinal Study of Ageing

Anna-Lena Elpers, Andrew Steptoe*

Department of Behavioural Science and Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK

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ABSTRACT

Despite extensive observational and intervention research, the association between concentrations of dehydroepiandrosterone sulfate (DHEAS) and cognition at older ages remains unclear. This study investigated cross-sectional and longitudinal relationships between plasma DHEAS and cognitive function in a large nationally-representative cohort of men and women aged 50 and older. Data were analysed from 5061 participants (mean age 65.1, standard deviation 8.61) who completed memory, verbal fluency and processing speed tests at baseline and two years later. Age, education, marital status, paid employment, depressive symptoms, mobility impairment, coronary heart disease and diabetes were included as covariates, and analyses were stratified by gender. We found positive associations at baseline between DHEAS concentration and aggregate cognition after adjustment for covariates in men ($\beta = 0.049$, standard error (s.e.) 0.020, $p = 0.015$). Longitudinally, DHEAS at baseline predicted cognition two years later in men ($\beta = 0.052$, s.e. 0.020, $p = 0.010$), but not after baseline cognition was taken into account ($\beta = 0.022$, s.e. 0.016, $p = 0.17$), indicating that DHEAS was not associated with rate of cognitive decline. Similar associations were recorded at 6 year follow-up. No significant relationships between DHEAS and cognition were observed among women. We conclude that greater DHEAS concentrations are associated with cognition level at older ages in men, but are unlikely to play a functional role in cognitive decline.

1. Introduction

Dehydroepiandrosterone sulfate (DHEAS) is an abundant steroid hormone in the human circulation. It is secreted primarily from the adrenal cortex, has a half life of 8−10 h, and shows marked decreases in concentration with age. Lower concentrations of DHEAS have been associated with increases in all-cause mortality, cardiovascular disease risk, depressive symptoms, and other outcomes, suggesting that higher concentrations are protective, particularly among men (Barrett-Connor et al., 1986; Hu et al., 2015; Mazat et al., 2001; Wu et al., 2017).

There has been widespread interest in the relationship between DHEAS and cognitive function among older people, stimulated by the possibility that supplementation might protect against cognitive decline. Mechanistic research has documented a range of neuroprotective actions of DHEAS through multiple processes including blockade of excitotoxicity, the promotion of neurogenesis, neurite growth and neuronal survival, stimulation of apoptosis, influences on catecholamine synthesis, anti-oxidant effects, and anti-inflammatory and anti-glucocorticoid processes (Maggio et al., 2015; Maninger et al., 2009). However, associations between DHEA or DHEAS concentration and cognitive function have been inconsistent. A review of 13 observational population studies concluded that while most cross-sectional analyses documented positive associations, few relationships were apparent with changes in cognitive function (Maggio et al., 2015). Another systematic review of a wider literature identified gender differences in the associations between DHEAS and different aspects of cognition (de Menezes et al., 2016).

The methodology of these studies has been variable. Several investigations have been statistically underpowered, with none involving sample sizes of more than 1,000. Recruitment in some studies has not been systematic, and few have incorporated the full range of covariates that potentially confound associations between DHEAS and cognitive function. We therefore carried out a larger scale evaluation of the relationship between DHEAS and cognitive performance in 5061 men and women aged 50 and older involved in a nationally representative population cohort. We included a number of covariates associated both

* Corresponding author at: Department of Behavioural Science and Health, University College London, 1-19 Torrington Place, London WC1E 7HB, UK.
E-mail address: a.steptoe@ucl.ac.uk (A. Steptoe).

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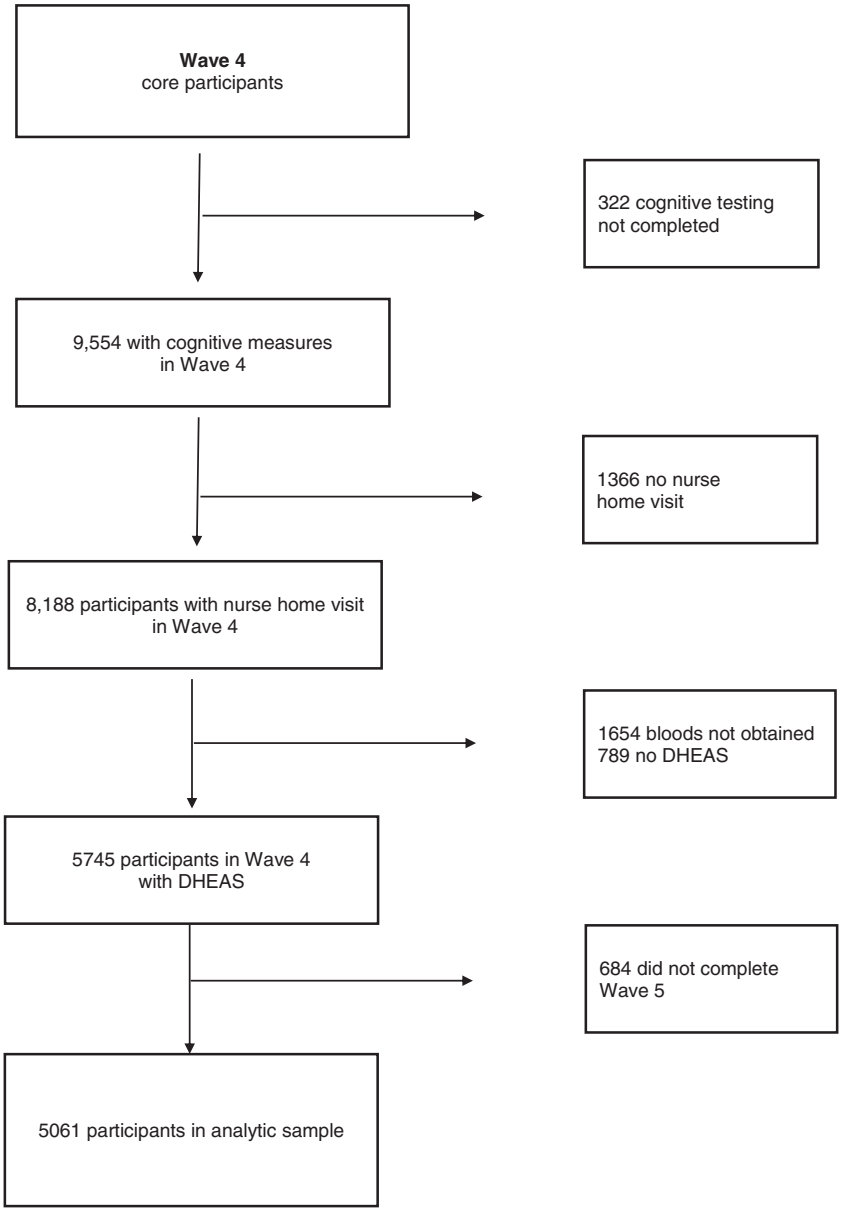

Fig. 1. Flow chart of participants in the study.

with DHEAS and cognitive function that could potentially confound the relationship, including sociodemogaphic factors, depressive symptoms, diabetes, coronary heart disease (CHD) and mobility impairment (Barrett-Connor et al., 1986; Hu et al., 2015; Sanders et al., 2010; Wu et al., 2017). Cross-sectional and longitudinal associations over a 2 year interval were tested, along with sensitivity analyses involving a 6-year follow-up period. In view of established differences in DHEAS concentrations in men and women, analyses were stratified by gender.

2. Methods

2.1. Participants

The data analysed in this report were derived from waves 4 (2008) and 5 (2010) of ELSA, a nationally representative sample of men and women aged 50 and older living in the community in England. The study is described in detail elsewhere (Steptoe et al., 2013), and full information is provided at http://www.elsa-project.ac.uk/. The study was approved by the National Research Ethics Service, and all participants provided informed consent. The flow chart of participants included in the study is shown in Fig. 1. There were 9886 core participants in wave 4, of whom 9554 completed cognitive tests during a computer assisted personal interview (CAPI) carried out by an interviewer in the respondents' own homes. After the CAPI was completed, participants were offered a nurse home visit for assessment of biomedical variables, but 1366 did not have this visit because of difficulty scheduling, refusal, or lack of availability. Of the 8188 who had a nurse visit, DHEAS measures were available from 5,745. The remainder did not have blood taken, or the DHEAS assay was unsatisfactory. Participants were contacted 2 years later for another CAPI and 5061 had repeat cognitive assessments, so form the analytic sample.

Compared with the participants excluded from the study, the analytic sample were slightly younger on average, were better educated, more likely to be married, and less likely to have health problems ($p < 0.001$).

2.2. Measures

2.2.1. Plasma DHEAS

Blood samples were collected from willing participants except when

they had a bleeding or clotting disorder, were taking anticoagulant drugs, ever had a fit, or did not agree with giving consent in written form. Plasma DHEAS was measured using an DCP Immulite 2000 analyser in the chemical pathology laboratories of the Royal Victoria Infirmary, Newcastle upon Tyne, UK.

2.2.2. Cognitive function

Three aspects of cognitive function were assessed in waves 4 and 5 of ELSA: memory (immediate and delayed recall), verbal fluency, and processing speed. In the memory test, participants were presented with a list of 10 words that were read out at the rate of one word for every 2 s. A total of four such lists were available, and these were randomly allocated by computer. After the presentation of words, participants were asked to recall as many words as they could (immediate recall). Participants were also asked to recall the words after an interval during which they completed other cognitive tests (delayed recall). The combined number of correctly remembered words was used as a measure of memory, but results were the same when the immediate and delayed recall were analysed separately. Verbal fluency was used as a measure of executive function. Participants were asked to name as many animals as they could in 1 min. Processing speed was measured using a letter cancellation task. Participants were given a page of random letters, and were asked to cross out as many target letters (P and W) as quickly and accurately as possible within one minute. The processing speed score was the total number of letters searched, so higher scores indicate faster processing. The cognitive tests used in ELSA are all standard measures used in other population studies, and take around 10 min to complete. These tests have been analysed extensively in previous work in ELSA on cognitive function in relation to coronary heart disease, inflammation and sleep, use of public transportation, loneliness, and other factors (Jackowska and Cadar, 2020; Reinhard et al., 2019; Yin et al., 2019; Xie et al., 2019).

2.2.3. Covariates

Covariates were selected a priori as potential confounders of associations between DHEAS and cognitive function. Age was modelled as a continuous variable. Education was classified into five categories based on highest qualification: no qualification; basic qualifications; high school graduation; further education; and university or college degree. Only 2.1 % participants were of non-White ethnicity, and ethnicity was unrelated to DHEAS concentration, so was not included as a covariate. Marital status, employment (employed vs. unemployed) and current smoking were binary variables. Depressive symptoms were measured using the 8-item Centre for Epidemiologic Studies Depression Scale (CES-D) (Steffick, 2000), a shortened scale with a Cronbach α of 0.78 in this sample. We used a score of ≥4 to indicate the presence of significant depressive symptoms, since this threshold has previously been validated against gold standard psychiatric interviews as reflecting clinically significant symptoms (Radloff, 1977). Mobility impairments were assessed with 10 items (e.g. climbing one flight of stairs without resting, picking up a small coin from a table). Prevalent coronary heart disease and diabetes were measured with self-reports of physician diagnoses.

2.3. Statistical analyses

Because of the known differences between men and women in plasma DHEAS concentrations, all analyses were stratified by gender. Comparisons between men and women were carried out using analysis of variance for continuously distributed and chi-square tests for binary variables. DHEAS concentrations were skewed, so data were logged (+1) before analysis. In view of the possible impact of hormone replacement therapy (HRT) on DHEAS concentrations, we assessed whether or not women were taking HRT at the time of blood sampling. A small proportion (5.2 %) of women were taking HRT, but there was no difference in DHEAS concentration between those who were and were not taking HRT. Including HRT in the analyses did not affect results, so HRT was not included in the final models.

Separate ordinary least squares (OLS) regressions were carried out for each of the cognitive outcomes. Normalised scores were used to allow for direct comparisons between tests. In addition, an aggregated measures of cognitive function was computed by averaging normalised individual test scores. Cross-sectional analyses included three models: In model 1, associations between DHEAS and cognitive function were only adjusted for age; model 2 additionally included demographic covariates (education, marital status and employment), while in model 3 we added health-related covariates (depressive symptoms, mobility impairment, CHD and diabetes). Results are presented as standardised regression coefficients (ß) with standard errors (s.e.). The longitudinal analyses regressed wave 5 cognitive function on DHEAS and other variables measured at wave 4. The three models were the same as in the cross-sectional analysis, but model 4 included the baseline level of the cognitive outcome as an additional covariate. We tested for nonlinear age associations by including age^2 in the analyses but no associations were significant so this was excluded from the final models.

A sensitivity analysis was carried out involving 6 year as opposed to 2 year follow-up from baseline, with data from wave 7 (2014) of ELSA. The letter cancellation task was not administered in wave 7, so cognition was indexed by memory, verbal fluency, and aggregate cognition.

3. Results

3.1. Participant characteristics

There were 2337 men and 2724 women in the analysis, with an average age at baseline of 65 years (Table 1). Men tended to have higher educational qualifications, were more likely to be married or cohabiting and in paid employment than women (all $p < 0.001$). Depressive symptoms and mobility impairments were more common among women, while men had a higher prevalence of CHD and diabetes. As expected, plasma DHEAS concentrations were higher on

Table 1
Participant characteristics. Means ± SD or N (%).

	Men N = 2337	Women N = 2724	P difference
Age	65.00 ± 8.50	65.28 ± 8.88	0.24
Education			
No qualifications	442 (18.9 %)	755 (27.7 %)	< 0.001
Basic qualifications	520 (22.3 %)	672 (24.7 %)	
High school	324 (13.9 %)	500 (18.4 %)	
Further education	471 (20.0 %)	374 (13.7 %)	
Degree or higher	580 (24.8 %)	423 (15.5 %)	
Married/cohabiting	1784 (76.3 %)	1664 (61.1 %)	< 0.001
Paid employment	982 (42.0 %)	859 (31.5 %)	< 0.001
Current smoking	287 (12.3 %)	354 (13.0 %)	0.52
Depressive symptoms	173 (7.4 %)	414 (15.2 %)	< 0.001
Mobility impairments (n)	1.18 ± 1.96	1.83 ± 2.28	< 0.001
Coronary heart disease	242 (10.4 %)	162 (5.9 %)	< 0.001
Diabetes	227 (9.7 %)	183 (6.7 %)	< 0.001
DHEA-S (log)	1.30 ± 0.45	1.01 ± 0.39	< 0.001
Aggregate cognition - baseline	0.010 ± 0.675	0.144 ± 0.693	< 0.001
Memory – baseline (n items)	10.49 ± 3.27	11.12 ± 3.45	< 0.001
Verbal fluency – baseline (n items)	21.78 ± 6.64	21.27 ± 6.45	0.006
Processing speed – baseline (n items)	288.38 ± 78.90	316.45 ± 85.44	< 0.001
Aggregate cognition – follow-up	−0.046 ± 0.719	0.085 ± 0.752	< 0.001
Memory – follow-up (n items)	10.32 ± 3.44	10.99 ± 3.66	< 0.001
Verbal fluency – follow-up (n items)	21.32 ± 6.79	21.07 ± 6.74	0.19
Processing speed – follow-up (n items)	288.03 ± 79.19	313.21 ± 84.51	< 0.001

Table 2
Cross-sectional associations between DHEA-S and cognitive function.

	Model 1		Model 2		Model 3	
	β (s.e.)	p	β (s.e.)	p	β (s.e.)	p
Men						
Aggregate cognition	0.078 (0.021)	< 0.001	0.061 (0.020)	0.002	0.049 (0.020)	0.015
Memory	0.066 (0.021)	0.002	0.051 (0.020)	0.012	0.035 (0.021)	0.088
Verbal fluency	0.070 (0.022)	0.002	0.056 (0.022)	0.009	0.049 (0.022)	0.025
Processing speed	0.040 (0.023)	0.086	0.031 (0.023)	0.19	0.030 (0.024)	0.21
Women						
Aggregate cognition	0.023 (0.018)	0.23	0.023 (0.018)	0.21	0.019 (0.018)	0.29
Memory	0.005 (0.019)	0.80	0.005 (0.018)	0.79	0.002 (0.018)	0.90
Verbal fluency	0.011 (0.019)	0.57	0.010 (0.019)	0.61	0.006 (0.019)	0.75
Processing speed	0.033 (0.021)	0.12	0.036 (0.021)	0.090	0.035 (0.021)	0.099

Model 1: DHEA-S adjusted for age.
Model 2: DHEA-S adjusted for age, education, marital status, and employment status.
Model 3: DHEA-S adjusted for age, education, marital status, employment status, smoking, depressive symptoms, mobility, CHD and diabetes.

average in men than women; the untransformed means were 3.09 ± 2.00 and 1.99 ± 1.31 μmol/l respectively. The gender differences in cognitive function were inconsistent; women had higher memory and processing speed scores than men, while men had higher verbal fluency than women at baseline but not follow-up.

Among men and women, plasma DHEAS correlated with all covariates except marital status ($p = 0.009$ to < 0.001). DHEAS concentrations were negatively associated with age, smoking, depressive symptoms, mobility impairment, CHD and diabetes, and positively related to education level and being in paid employment. A similar pattern was seen among women, except that the association with depressive symptoms was not significant, while DHEAS was higher among married than unmarried women ($p < 0.001$).

3.2. Cross-sectional associations

Plasma DHEAS levels were positively associated with aggregate cognition, memory, and verbal fluency, but not with processing speed among men (Table 2). Individuals with higher DHEAS had better memories, executive function and aggregate cognition after adjusting for age and demographic characteristics including education. When health-related variables were included in model 3, associations between DHEAS and aggregate cognitive function ($p = 0.015$) and verbal fluency ($p = 0.025$) remained robust, but the relationship with memory was no longer significant. None of the associations between DHEAS and cognitive function were significant among women.

3.3. Longitudinal associations

Over the two year period, there was a significant decline in memory among men ($p = 0.010$) and women ($p = 0.008$), and in verbal fluency ($p < 0.001$ and 0.024 for men and women respectively). Processing speed diminished in women ($p = 0.001$), but not men ($p = 0.46$). The longitudinal associations between baseline DHEAS and cognitive function two years later are summarized in Table 3. As in the cross-sectional results, aggregate cognition, memory and verbal fluency on follow-up were associated with DHEAS after age and demographic factors were taken into account (models 1 and 2). After adjustment for health-related factors, the relationship with memory was no longer significant (model 3). But when baseline levels of cognitive function were included as covariates (model 4), none of the associations with DHEAS remained. This indicates that DHEAS is correlated with the level of cognitive function, but not with changes over time. As in the cross-sectional analyses, these associations were apparent in men but not women.

The sensitivity analysis involved 6 year follow-up of cognition to ensure robustness of findings. We found no evidence of associations between DHEAS and changes in cognition over this time period (Table 4).

4. Discussion

This large population-based study of older men and women investigated the association between plasma DHEAS concentration and cognitive function both cross-sectionally and over a 2 year longitudinal period. We found cross-sectional associations between higher DHEAS and better cognitive function among men but not women. The relationship was partly explained by sociodemographic and health-related factors; taking these factors into account statistically reduced the age-adjusted association between DHEAS and aggregate cognition by around 37 % (Table 2). Longitudinally, baseline DHEAS was positively related to cognition two years later, but this link was no longer significant when baseline cognition was taken into account. The longitudinal results therefore provide no evidence at DHEAS concentration is related to rate of cognitive decline over time. Similar patterns emerged when cognition was assessed 6 years after baseline.

Our observation of an association between DHEAS and cognitive function in men but not women is consistent with some but not other previous work (Goldman and Glei, 2007; Hildreth et al., 2013; Sanders et al., 2010). Some studies showing positive relationships in women have involved a rather larger age range than here, with the inclusion of young adult participants (Davis et al., 2008). The concentration of DHEAS is greater at older ages in men than women, and there is evidence that it may show more pronounced protective relationships with other health outcomes in men as well (Goldman and Glei, 2007; Ohlsson et al., 2015; Veronese et al., 2016).

There were marked differences in associations between DHEAS and different cognitive tests. Although the cross-sectional relationship between aggregate cognition and DHEAS was significant after adjustment for sociodemographic and health-related covariates, the link with memory was not longer reliable after health-related factors had been taken into account. Processing speed was also unrelated to DHEAS concentration. Other studies have found differences in associations between DHEAS and different memory tests in men, suggesting that some show more robust relationships than others (Hildreth et al., 2013). The processing speed measure indexed rate of performing letter cancellation rather than accuracy, so may not reflect the efficiency of visual search (Geldmacher and Riedel, 1999). Many previous studies have used aggregate measures of cognitive function such as the Mimi-Mental State Examination rather than specific tests, and the literature on associations with individual cognitive capacities been quite variable (Barrett-Connor and Edelstein, 1994; Fonda et al., 2005; Valenti et al., 2009; Yaffe et al., 1998).

Our analyses showed no association between DHEAS and future cognitive function after baseline performance had been taken into

Table 3
Longitudinal associations between DHEAS and cognitive function.

	Model 1		Model 2		Model 3		Model 4	
	β (s.e.)	p	β (s.e.)	p	β (s.e.)	p	β (s.e.)	p
Men								
Aggregate cognition	0.080 (0.021)	< 0.001	0.065 (0.020)	0.001	0.052 (0.020)	0.010	0.022 (0.016)	0.17
Memory	0.063 (0.021)	0.003	0.050 (0.020)	0.014	0.036 (0.021)	0.081	0.019 (0.018)	0.29
Verbal fluency	0.066 (0.022)	0.002	0.056 (0.021)	0.009	0.048 (0.022)	0.027	0.019 (0.017)	0.27
Processing speed	0.051 (0.020)	0.033	0.041 (0.024)	0.084	0.032 (0.024)	0.18	0.013 (0.020)	0.53
Women								
Aggregate cognition	0.003 (0.018)	0.86	0.004 (0.018)	0.23	0.001 (0.018)	0.99	−0.012 (0.014)	0.40
Memory	0.006 (0.019)	0.75	0.007 (0.018)	0.68	0.003 (0.018)	0.88	0.002 (0.016)	0.92
Verbal fluency	−0.001 (0.019)	0.96	−0.002 (0.019)	0.94	−0.003 (0.019)	0.90	−0.005 (0.015)	0.73
Processing speed	0.012 (0.021)	0.055	0.014 (0.022)	0.53	0.010 (0.024)	0.64	−0.012 (0.018)	0.51

Model 1: DHEA-S adjusted for age.
Model 2: DHEA-S adjusted for age, education, marital status, and employment status.
Model 3: DHEA-S adjusted for age, education, marital status, employment status, smoking, depressive symptoms, mobility, CHD and diabetes.
Model 4: DHEA-S adjusted for age, education, marital status, employment status, smoking, depressive symptoms, mobility, CHD, diabetes, and baseline cognitive function.

account, although the relationship was significant before baseline cognition had been added to the analyses (Table 3). This indicates that the prospective association was a reflection of cross-sectional correlations rather than cognitive decline. The lack of longitudinal association replicates findings from other cohort studies with smaller sample sizes such as the Baltimore Longitudinal Study of Aging, the Rancho Bernardo Study, and the Rotterdam study (Barrett-Connor and Edelstein, 1994; Kalmijn et al., 1998; Moffat et al., 2000). Studies in nonhuman primates have also shown little association between DHEAS and cognition during ageing (Herndon et al., 1999). There are, however, well conducted studies that have shown prospective associations between DHEA or DHEAS and cognitive changes over time (Goldman and Glei, 2007; Valenti et al., 2009). The explanation is unclear. Goldman and Glei (2007) analysed data from he Taiwanese Social Environment and Biology of Aging Study, but did not include education or other indicators of socioeconomic status in their models. Lower DHEAS was also associated with accelerated cognitive decline in the InChianti Study (Valenti et al., 2009). The Italian sample was characterised by low educational levels with average schooling of only 5 years, whereas in our study the majority of participants had been educated up to mandatory schooling ages in England (14 or 15 years depending on age). It is possible that DHEA has more prominent effects in a low education environment.

Our study benefitted from a large, well characterised, representative sample, and included a range of covariates. The specific measures evaluated in this analysis were part of a much larger array of economic, social, psychological, health, and biological assessments, eliminating the chance that participants were aware of the specific hypotheses under investigation. However, this is an observational study, so causal conclusions cannot be drawn. The study sample was predominantly of white European ancestry, and results may not generalise to other groups. The range of cognitive tests was limited, and assessment of a broader range of capabilities would have been desirable. Plasma DHEAS was measured on only one occasion, and we did not have concurrent assays of cortisol, so we could not analyse the ratio between these hormones. Measures of testosterone would also have been valuable in view of the role played by testosterone in sustaining DHEAS concentration (Sorwell et al., 2014). It should also be noted that DHEAS in the brain is thought to be predominantly synthesised locally, and concentration in the peripheral circulation may not reflect levels in the brain (Maninger et al., 2009). Nevertheless, our findings contribute to the literature in documenting in the largest sample yet studied cross-sectional associations between plasma DHEAS and cognition in men. Since DHEAS was not related to cognitive decline over time, the results imply that the hormone is one component of a healthier endocrine profile rather than contributing directly to cognitive performance. In conjunction with the inconclusive findings from supplementation trials of both men and women (Grimley Evans et al., 2006; Davis et al., 2011), our results provide no support for DHEAS playing a functional role in cognitive decline.

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The English Longitudinal Study of Ageing was developed by a team

Table 4
Longitudinal associations between DHEAS and cognitive function – 6 year follow-up.

	Model 1		Model 2		Model 3		Model 4	
	β (s.e.)	p	β (s.e.)	p	β (s.e.)	p	β (s.e.)	p
Men								
Aggregate cognition	0.041 (0.023)	0.074	0.028 (0.022)	0.22	0.011 (0.022)	0.64	−0.011 (0.020)	0.57
Memory	0.060 (0.023)	0.01	0.045 (0.022)	0.042	0.030 (0.022)	0.18	0.011 (0.020)	0.60
Verbal fluency	0.014 (0.024)	0.57	0.004 (0.024)	0.87	−0.016 (0.024)	0.67	−0.031 (0.021)	0.13
Women								
Aggregate cognition	0.021 (0.020)	0.29	0.015 (0.019)	0.77	0.009 (0.019)	0.65	0.001 (0.017)	0.94
Memory	0.005 (0.020)	0.81	0.001 (0.020)	0.99	−0.006 (0.020)	0.77	−0.009 (0.017)	0.61
Verbal fluency	0.030 (0.021)	0.16	0.024 (0.020)	0.23	0.018 (0.020)	0.36	0.016 (0.018)	0.35

Model 1: DHEA-S adjusted for age.
Model 2: DHEA-S adjusted for age, education, marital status, and employment status.
Model 3: DHEA-S adjusted for age, education, marital status, employment status, smoking, depressive symptoms, mobility, CHD and diabetes.
Model 4: DHEA-S adjusted for age, education, marital status, employment status, smoking, depressive symptoms, mobility, CHD, diabetes, and baseline cognitive function.

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Declaration of Competing Interest

Neither of the authors have any conflicts of interest to declare related to the findings of this study.

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