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# Higher serum dehydroepiandrosterone sulfate protects against the onset of depression in the elderly: Findings from the English Longitudinal Study of Aging (ELSA)

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ABSTRACT

Depression is one of the major causes of disability worldwide, but the complete etiology of depression is not fully understood. Dehydroepiandrosterone (DHEA) and its sulphated form DHEA(S) have been associated with mood and healthy aging. Associations with mental illness over the middle to late years of life have not yet been extensively investigated in large, western community-dwelling samples. The aim of this study was to investigate whether low DHEA(S) levels are associated with the development of depressive symptoms in a large longitudinal cohort study of older men and women. We assessed data from English Longitudinal Study of Aging (ELSA) to evaluate the association of DHEA(S) levels and depressive symptoms measured by Center for Epidemiologic Studies Scale (CES-D) at baseline ($n = 3083$) and at 4-year follow-up ($n = 3009$). At baseline, there was an inverse association between DHEA(S) and depressive symptoms ($B = -0.252$, $p = 0.014$). Adjustments for physical illnesses, impairments in cognitive function and health behaviors abolished this association ($p = 0.109$) at baseline. Decreased DHEA(S) levels at baseline also predicted incident depression at 4-year follow-up ($B = -0.332$, $p < 0.001$). In conclusion, higher DHEA(S) levels were associated with reduced risk of developing depressive symptoms in both men and women.



## 1. Introduction

Depression is the second major cause of disability worldwide affecting around 350 million people (WHO, 2009). Although the precise etiology of depression is complex and remains unclear, there is evidence that the prevalence of depressive disorder increases with age (Samaras et al., 2013) and affects around 17% of the elderly population (Luppa et al., 2010).

Dehydroepiandrosterone (DHEA) is a steroid hormone mainly synthesized in the adrenal glands in response to adrenocorticotrophic hormone, although *de novo* synthesis in the brain has also been described (Maninger et al., 2009; Sugaya et al., 2015). DHEA and its sulphated form DHEA(S) are the more prevalent circulating steroid hormones, acting as precursors of the sexual hormones, as a neurosteroid, and it is hypothesised to present opposite effects to glucocorticoids (Maurice et al., 1996; Kimonides et al., 1999; Binello and Gordon, 2003; Maninger et al., 2009; Moriguchi et al., 2013). DHEA has been described as a modulator of neurotransmission as it can affect serotonin, γ-amino butyric acid (GABA), glutamate, and dopamine levels (Kimonides et al., 1998; Robichaud and Debonnel, 2004; Traish et al., 2011). Studies demonstrate that DHEA presents a strong age-related decline (Berr et al., 1996; Kroboth et al., 1999), and thus may help explain age related increases in depression.

The role of DHEA(S) in depression is still poorly understood. In clinically diagnosed depressed patients the role DHEA(S) plays is still inconclusive, as studies showing increased (Assies et al., 2004; Morita et al., 2014), decreased (Kurita et al., 2012; Lopes et al., 2012) and no changed levels have been found (Erdinçler et al., 2004). In the population, most cross-sectional studies report that lower DHEA(S) levels are associated with poor mental health (Haren et al., 2007; Wong et al., 2011; Michikawa et al., 2013) although no association has also been reported (ó Hartaigh et al., 2012). The role of gender on this association is still inconclusive (Berr et al., 1996; Michikawa et al., 2013).

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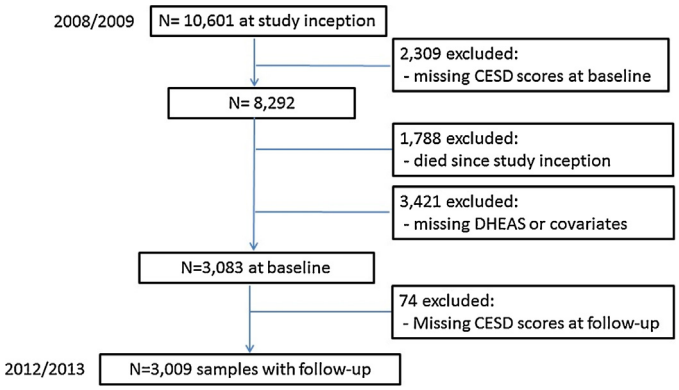


**Fig. 1.** Analytical sample flowchart.

Few prospective studies have been conducted and are comparatively small in sample size or have analysed women or men exclusively. These studies seem to point toward an association of lower DHEA(S) levels with incident depression (Berr et al., 1996; Goldman and Glei, 2007; Michikawa et al., 2013; Veronese et al., 2015). The aim of this study was to investigate whether lower DHEA(S) levels predicts the development of depressive symptoms in a large community-dwelling sample of older men and women.

## 2. Methods

### 2.1. Study population

The English Longitudinal Study of Aging (ELSA) is a longitudinal study of men and women aged 50 and over, and is representative of people living in England (Steptoe et al., 2013). Objective and subjective data relating to health and disability, biological markers of disease, economic circumstances, social participation, networks and well-being were collected. ELSA aims to measure outcomes across a wide range of domains and to provide high-quality multidisciplinary data that can shed light on the causes and consequences of outcomes of interest. Wave 1 was collected in 2002/3, and participants are followed-up every 2 years, with a nurse visit and biomarker assessment every four years (http://www.ifs.org.uk/ELSA). Participants gave full informed consent to participate in the study and ethical approval was obtained from the London Multi-center Research Ethics Committee. For the purposes of the present analyses, data collected at wave 4 (2008/9) were used as the baseline.

For the present study, 10,601 people participated in the study. Since 2008, 1788 people had died by 2013 follow-up period and were therefore not included in the analysis. 2309 were excluded due to missing depressive symptoms scores at baseline. Moreover, 3421 participants were excluded because there were no information about DHEA(S) and/or covariates. We have excluded participants with doctor-diagnosed dementia. Thus, at baseline there were 3083 people. Seventy-four participants did not have CESD scores at follow-up. At follow-up the analytical sample consisted of 3009 participants eligible for analysis. Selection of the analytical sample is represented in Fig. 1.

Compared to those study members who featured in the analytical sample, people with missing data were more likely to be female ($X^2 = 20.75$, $P < 0.001$), smokers ($X^2 = 26.27$, $P < 0.001$), on the lowest tertile of wealth ($X^2 = 12.20$, $P < 0.001$), to report higher depressive symptoms (total sample $1.40 \pm 1.90$, analytical $1.11 \pm 1.70$, $p < 0.001$), be inactive ($X^2 = 41.71$, $P < 0.001$), and have higher frequency of cognitive impairment (total score total sample $29.77 \pm 6.99$, analytical sample $31.21 \pm 5.73$, $p < 0.001$). However, no more likely to have diabetes, cardiovascular disease, stroke or cancer ($X^2 = 0.199$, $P = 0.348$), be obese ($X^2 = 0.83$, $P = 0.402$) or consume alcohol ($X^2 = 4.337$, $P = 0.114$).

### 2.2. Assessment of depressive symptoms

Depressive symptomatology was measured using the eight-item Center for Epidemiological Studies-Depression (CES-D) scale, a widely used measure that identifies people "at risk" of depression in population surveys (Radloff, 1977; Turvey et al., 1999). The psychometric values of the eight-item CES-D are comparable to those of the full 20-item CES-D (Steffick, 2000). We derived a summary CES-D score by adding responses to all eight dichotomous questions (possible range: 0–8). To exclude cases of elevated depressive symptoms that are possible cases of clinical depression at baseline, we dichotomized the summary score around the cut point of four or higher, a conservative threshold that corresponds to the cut point of 16 or higher on the 20-item CES-D (Steffick, 2000) in our longitudinal analysis.

### 2.3. Assessment of DHEA(S)

Blood samples were taken from willing ELSA core members, except those who had a clotting or bleeding disorder (e.g., hemophilia or low platelets), had ever had a fit, were not willing to give their consent in writing or were currently on anticoagulant drugs (e.g., warfarin therapy).

DHEA(S) was only collected at baseline. The analysis of the blood data was carried out in the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). The analysis of DHEA(S) levels from serum was performed using the Roche DHEA(S) assay that is a competitive immunoassay using electrochemiluminescence technology (analytical range: 0.003–27 μmol/L). During the first incubation step DHEA(S) binds with a biotinylated monoclonal DHEA(S)-specific antibody. During the second incubation a DHEA(S) derivative labeled with a ruthenium complex occupies the remaining free binding sites on the biotinylated antibody. The entire complex becomes bound to the streptavidin-coated microparticulate solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated in to the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are removed using Procell. Application of a voltage to the electrode induces chemiluminescent emission that is measured by a photomultiplier. Results are determined by measuring the electrochemiluminescence signal obtained from the reaction product of the sample against a calibration curve generated by 2-point calibration and a master curve provided via the reagent barcode. Detailed information on the technicalities of the blood analysis, the internal quality control and the external quality assessment for the laboratory have been described elsewhere (Graig et al., 2006).

### 2.4. Measurement of covariates

Participants' age, gender and BMI were assessed during a face-to-face visit in the home. Height and weight, which were assessed by a nurse, were used to calculate body mass index (BMI, $kg/m^2$). Socioeconomic status 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). Cohabitation was defined as currently living alone or not. Cognitive function was assessed using a test of memory and executive function (Steel et al., 2003). Self-reported health behaviors included smoking status (current, ex-smoker/never), frequency of alcohol consumption in the past