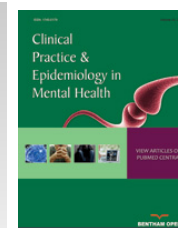




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Dehydroepiandrosterone, Its Sulfate and Cognitive Functions

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Abstract:

To present a review of cross-sectional and longitudinal studies that investigate the relationship between the hormones Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone sulfate (DHEA-S) and cognition. Methods: The cognition items included in this review were global cognitive function, memory, attention, executive function, intelligence, perception and visuospatial ability. A systematic review was proceeded using three databases: PubMed, ISI Web of Science, and PsycINFO. Results: Two thousand fifty five references about cognition and hormones were found; 772 duplicated references were excluded, resulting in 1.283 references to be evaluated. According to exclusion and inclusion criteria, 25 references were selected. A positive correlation between DHEA-S blood levels and global cognition was found in women and men. Other positive correlations between DHEA-S and working memory, attention and verbal fluency were found only in women. The DHEA effect on cognition is limited to one study conducted among young men with high-doses.

Keywords: Attention, Cognition, Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate, Executive Function, Memory, Neuropsychology.

1. INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are two active androgens mainly produced by the adrenal glands. DHEA is the main pro-hormone related to biosynthesis of testosterone and estrogen [1 - 4]. Studies have shown that these hormones are not synthesized just by the gonads and adrenal glands of men and women [1, 2]. DHEA is also produced in brain regions, being recently considered a neurosteroid [3]. Although there is still debate on DHEA receptors in brain, these findings corroborate the evidence that DHEA is not just a pre-hormone from adrenals, but rather a hormone in its own right, and that it modulates a series of biological processes, with a remarkable tropism for the central nervous system [5].

DHEA-S is a protective anabolic hormone with an important role in maintaining and restoring the human organism. It is known for its antioxidant activity and ability to help in neuronal preservation. DHEA-S is originated in the zona reticularis area of the adrenal cortex in response to adrenocorticotrophic hormone (ACTH). As DHEA, has a higher production between 25 and 35 years old and then gradually decrease over time [6, 7]. Sex difference in DHEA-S levels remains unclear, while most studies reported higher levels in men than in women, others studies did not found differences [7 - 9].

The effects of DHEA and DHEA-S on cognitive functions have been targeted in all fields [10 - 12]. In a study that assessed the relationship between sex hormones and cognition, it was found that DHEA-S is positively associated with

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executive function and memory [13]. However, a literature review in the period of time between 1994 and 2013 observed that despite cross-cohort studies point to evidence of relationship between DHEA-S and cognition, RCTs and longitudinal studies were not able to consistently confirm these evidences [14]. Besides, the long term risk-effects remain unclear [15, 16].

Cognitive functions are organized by classes, similar to the operation of a computer. There are input, storage, processing and output classes [17 - 21] and each of these functional classes comprises of many discrete activities as perception, memory, attention, executive function and intellectual function [21 - 23]. One way to access the development and integrity of cognitive function is through neuropsychology, which is the study of the relationship between brain and behavior [23, 24]. Neuropsychological evaluation is a way of investigating different cognitive functions and their relations with brain function and its neurochemical factors, such as DHEA and DHEA-S.

Considering the recent speculation about the relationship between cognition and DHEA and DHEA-S, this paper aims to review the relationship between DHEA, DHEAS and cognitive functions.

2. METHODS

A systematic search of the literature was proceeded in PubMed, ISI Web of Knowledge and PsycINFO, using the terms: Dehydroepiandrosterone, Dehydroepiandrosterone sulfate, DHEA, DHEAS, cognition, cognitive function, memory, attention, executive function, intelligence, perception, visuospatial ability. All combinations between the first four terms for the specific hormones of this review were crossed with each specified mental function. The last search was proceeded in October 2015 and no time restriction was used. Two thousand and fifty three references were found (PubMed, 1217; The study selection process obeyed the following steps: Database search; exclusion of repeated references; summary analysis; exclusion of articles deemed ineligible after reading the summaries; full analysis of potentially eligible articles; exclusion of articles considered ineligible after complete reading; and the final selection of studies considered suitable to compose this review (Fig. 1).

References analyzed were included if they met the inclusion criteria: 1) report at least one cognitive function assessed by neuropsychological measures and 2) report clinical or community-based studies with populations that had DHEA or DHEA-S levels assessed. The exclusion criteria were: 1) review papers; 2) studies that included population with genetic syndromes (such as Down syndrome, Turner's disorder, and Klinefelter's), severe cognitive impairment (such as schizophrenia, dementia, and epilepsy) and endocrine diseases (such as polycystic ovary syndrome, androgen insensitivity syndrome and others); 3) studies with animals. After abstract analysis, 25 references were selected for this review (Table 1).

Methodology was based on the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA), which addresses conceptual and practical advances in systematic reviews [25].

3. RESULTS

3.1. Cognitive Functions Assessed

Despite growing knowledge about the role of DHEA and DHEA-S in the central nervous system, the majority of the research has focused on manifestations of sexual disorders, mood and aging [16 - 20] rather than the assessment of the relationship between these hormones and cognitive functions [18, 19].

In this review, the most evaluated topics were global cognition (n=13 articles) and memory (n=11), followed by attention (n=4), executive function (n=3), intelligence (n=2), perception (n=1) and visuospatial ability (n=1). Several studies evaluated more than one cognitive function.

3.1.1. Global Cognition

Cognitive functions constitute a set of the basic elements of cognition such as: perception, learning, memory, attention, vigilance and reasoning among others [21, 26]. Through cognition humans are able to process all information stored in brain [26]. Fourteen articles addressed the relationships between DHEA, DHEA-S and global cognition. Concerning the endogenous levels of DHEA and/or DHEA-S, 12 articles were found.

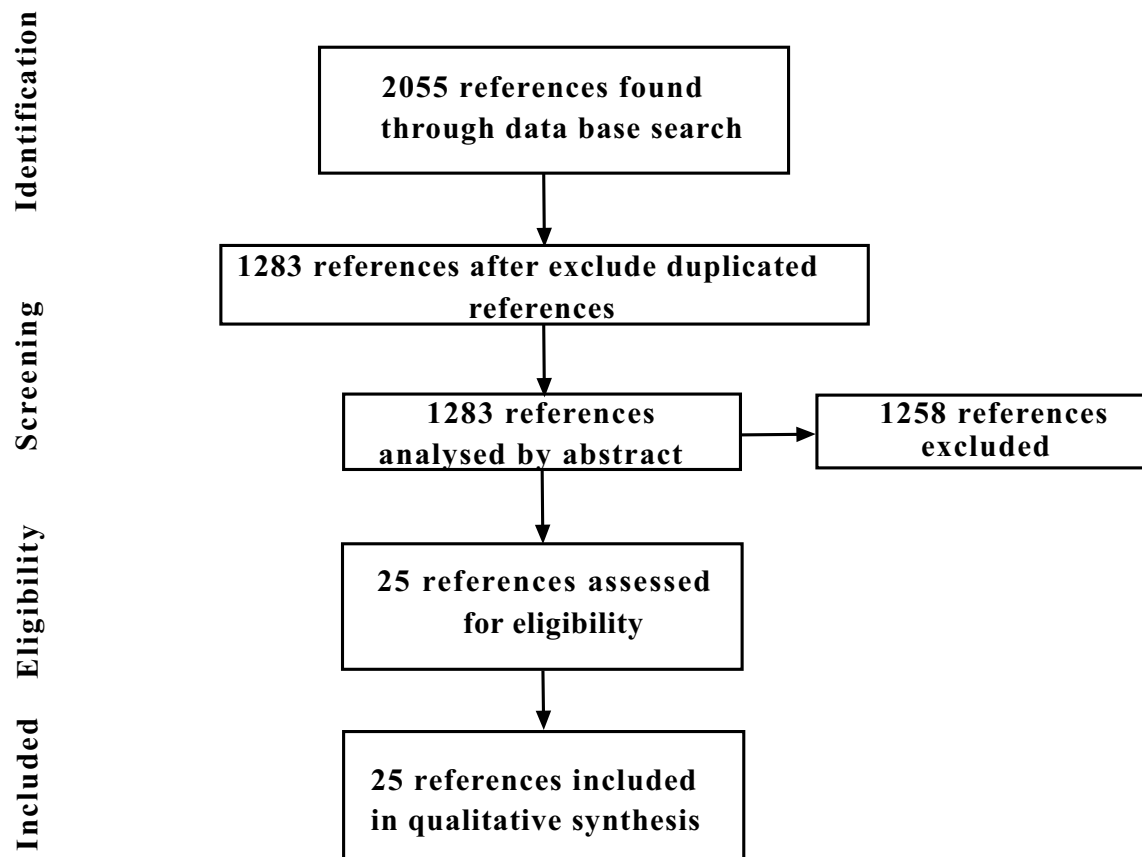


Fig. (1). Flowchart of the different phases of the systematic review.

3.1.1.1. Correlations in Both Genders Samples

In a cross-sectional evaluation of healthy elderly subjects ($n=313$; women, mean age, 77.3 ± 6.4 years; men, mean age, 76.7 ± 5.4 years), the Mini-Mental State Examination (MMSE) was presented and blood samples were collected. The results showed that DHEA had a negative correlation with cognitive function in women ($b=-.79$, $p=.03$) [5].

Two articles from the same research group using the same sample and battery of tests showed: In the first study, 967 elderly Taiwanese were evaluated and blood and urine samples were collected. DHEA-S was positively associated with cognitive function in women [27]. In the second study, these authors compared the results of previous evaluations from the same sample in 836 elderly patients. This time, a positive correlation was found between DHEA-S and cognitive function in 86% of the male sample ($r= -0.0016$, $p < 0.001$) [28]. Corroborating this last finding, in a study among older elderly Japanese adults ($n=208$) assessed by the Hasegawa Dementia Scale - Revised, blood levels of DHEA-S were associated with better cognitive function in men [29].

Another study, published into two papers, evaluated 86 elderly people using an extended neuropsychological battery. Both transversal and longitudinal assessments did not show any correlations between hormones and cognition [30, 31]. Similarly, another study using elderly subjects ($n=145$) failed to find any correlation between hormonal levels and MMSE scores [32].

3.1.1.2. Correlations in Male Samples

A cross-sectional study of elderly African men ($n=124$), using the multiple linear regression model, found that higher levels of DHEA-S, measured from blood samples, were associated with higher scores of MMSE ($b=.098$; $p=.008$) [9]. The other study evaluated 883 men for a period of 31 years period. DHEA-S blood levels were measured, and neuropsychological assessments were performed every two years. The comparison between the first and the last assessments found no statistically significant associations between DHEA-S levels and cognition [10].

3.1.1.3. Correlations in Female Samples

A cross-sectional study of DHEA-S using MMSE compared healthy elderly women (n=103) with a control group of healthy young women (n=25). Significantly ($p<0.01$) lower concentrations of DHEA-S were observed in women with lower MMSE scores compared to those with higher MMSE scores [33]. Another study aimed to evaluate the association between the decline of blood levels of DHEA-S and cognitive functions over the years. Elderly women (n=394) were assessed using the MMSE and neuropsychological tests at baseline and 4-6 years later. No associations were found between the cognitive performance and DHEA-S [11]. Similarly, a study assessing transversal and longitudinal global cognition in 218 Australian post-menopausal women through a composite derived from standardized scores of 17 individual test scores, found no significant relations between levels of DHEA-S and cognitive function [34].

3.1.1.4. Intervention Studies

In the first paper, MMSE was used for evaluation and 1 mg of dexamethasone was administered for 1 year and 9 months to elderly men and women (n=189). DHEA-S blood levels were measured before and after this medication and no statistically significant relationships were found between the hormone levels and cognitive impairment [33]. The longitudinal study, in which only postmenopausal women (n=20) received DHEA supplementation (25 mg) for 6 months, showed different results. A battery of tests was administered at the beginning (T1) and at the end (T2) of the treatment period. DHEA, DHEA-S and cortisol levels from blood samples were also measured. DHEA-S and the cortisol/DHEA ratios appeared to be negatively correlated with cognition before and after supplementation [36].

Although some studies have shown a positive correlation between DHEA and cognition, others have shown negative correlations, indicating that these relations are not yet clear. Two cross-sectional studies revealed a positive correlation between the DHEA-S levels and global cognition in women, whereby the first study used a battery of neuropsychological tests [27] and the second study used MMSE [33]. The cross-sectional study using MMSE showed a negative correlation between DHEA and cognition in women [5]. In the male population, 3 studies showed a positive correlation with DHEA-S among older men [9, 28, 29]. Seven studies failed to observe any connection between hormonal levels and cognition [10, 11, 30 - 32, 34, 35] and one identified negative correlations in women [36].

3.1.2. Memory

Memory is a function that gives meaning to time, maintains one's identity and ensures learning [23]. The complex process of memory requires a number of successive stages and it cannot be construed as a solitary system. Memory can be divided into working memory, declarative memory, procedural memory, short-term memory, long-term memory, and others [37, 38]. In this sample, 11 articles included have addressed memory. Four articles focusing on the endogenous levels of DHEA or DHEA-S and 7 articles are on DHEA supplementation.

3.1.2.1. Correlations in Both Genders Samples

The first cross-sectional study, using a sample of healthy elderly adults (n=313) assessed by memory components of the MMSE, showed that episodic declarative memory was negatively correlated with DHEA blood levels in women [5]. Another cross-sectional study, only with women (n=295 between the ages of 21 and 77 years), suggested a positive relationship between DHEA-S levels and working memory [39].

3.1.2.2. Correlations in Male Samples

One study was performed in 25 elderly men to assess long-term verbal memory. No correlation was found with DHEA-S blood levels in men [40]. Similarly, a survey of 981 elderly men showed no correlation between DHEA-S or DHEA blood levels and working memory [12].

3.1.2.3. Intervention Studies

Three of these studies were conducted using only male subjects. The first study evaluated 46 men. They received 50 mg DHEA daily for 13 weeks followed by placebo for 13 weeks, or the reverse. Salivary cortisol and DHEA levels were measured and cognition was assessed using Word List Memory and Object Location Memory. No significant effects of DHEA were observed in any of the trial outcomes, providing no support for benefits of DHEA supplementation for episodic declarative memory, despite the significant increase of DHEA levels after treatment [41]. Similarly, 17 elderly men on placebo or DHEA (50 mg/day) for 2 weeks (double blind) did not enhance their declarative and visual memory [42]. However, the last study showed that DHEA supplementation can influence on

memory aspects. The sample composed of young men (n=24) had the episodic memory assessed after daily DHEA supplementation (300 mg for 7 days). Significant effects when compared to the placebo group were found [43].

Studies comprising only of women showed different results. The first study, conducted among postmenopausal women (n=6), demonstrated that DHEA supplementation influenced memory. This sample was treated with 50 mg of DHEA daily for 4 weeks and showed negative effects of androgens on recognition memory. Recognition memory was observed to be negatively correlated to the level of ANDRO factor [44]. The second longitudinal study, using a daily dose of 50 mg of DHEA for 4 weeks, did not lead to short-term memory improvements in postmenopausal women (n=48) [45].

Two other studies comprised of men and women. Divided into control and treatment groups, 111 men and 118 women (mean age 68.7±7.9) received 50 mg of DHEA or placebo for one year. These groups were assessed using the Word List Memory and Word List Recall tests. No difference was found between groups in terms of changes in declarative memory [46]. Another study with 40 elderly men and women also found no effect on memory after DHEA supplementation [47].

Results regarding memory demonstrated a correlation between working memory and DHEA-S in women in just one cross-sectional study [39]. One longitudinal study, which focused on DHEA supplementation, demonstrated a negative correlation between DHEA and recognition memory in women [44], whereas other studies failed to demonstrate the effects of hormonal supplementation on working memory and episodic declarative memory [45 - 47]. In men, the majority of studies showed no relationship between DHEA or DHEA-S and all types of memory functions [5, 12, 40 - 42, 46, 47]. The only study that demonstrated a correlation between DHEA and memory was a longitudinal study, which used a higher DHEA dose supplementation (300 mg for 7 days) in young males [43]. All other studies that failed to demonstrate effects were conducted with a 50 mg daily dose [41, 42, 44 - 47].

3.1.3. Attention

Among the articles included in this review, 4 articles evaluated attention. Attention is a cognitive function defined as the ability to target and select information, inside and outside of the body, to maintain vigilance and organize behavior and mental processes [37, 38]. It is also defined as the direction of consciousness or a state of mental concentration about a specific object [49]. Attention is considered a multifaceted system and some authors subdivide it in focused attention; selective attention; response selection and executive control; and sustained attention [22, 38, 49].

3.1.3.1. Correlations in Female Samples

One cross-sectional study that assessed attention in women (n=295; age range, 21-77 years) found that DHEA-S blood levels are positively correlated with attention [39]. Another cross-sectional study conducted in elderly men (n=981) showed no correlations with DHEA or DHEA-S [12].

3.1.3.2. Intervention Studies

A longitudinal study of postmenopausal women (n=6) identified a negative relationship between the variable ANDROfactor and attention [44]. The longitudinal study conducted on 40 elderly subjects from both genders found no significant effect of 50 mg DHEA for two weeks on attention [47].

Again, a positive correlation was found only in a cross-sectional study with women [39], but not in the cross-sectional study with men [12]. Longitudinal studies with DHEA replacement showed no effects on either men and women [47] or even a negative relationship between androgens and attention [44].

3.1.4. Executive Function

Executive function is a set of skills that allows individuals to perform and control operations and to regulate information in the brain. Executive function can be divided into working memory, planning, problem solving, decision making, inhibitory control, fluency, cognitive flexibility, categorization, and others [23, 38]. The assessment of executive function was performed in 3 studies; one study reporting endogenous levels and 2 studies reporting DHEA supplementation.

3.1.4.1. Correlations in Female Samples

The cross-sectional study of a sample of 295 women (age range, 21-77 years) used the Controlled Oral Word

Association Test (FAS) to assess verbal fluency, which is an executive function. Higher DHEA-S blood levels corresponded with higher FAS scores, indicating a positive correlation between verbal fluency and DHEA-S [39].

3.1.4.2. Intervention Studies

Two longitudinal studies [46, 47] with mixed populations did not find any relationship between DHEA supplementation and an improvement of the executive functions. In the first study, 110 men and 115 women (mean age, 68.7 ± 7.9 years) were divided into treatment and placebo groups. The treatment group received 50 mg of DHEA for one year [46]. In the second study, 25 elderly men and 15 elderly women received two weeks of 50 mg of DHEA. Analyses showed no significant correlations [47].

The types of executive function studied in the articles were verbal fluency, categorization and cognitive flexibility. As observed in other cognitive functions, the cross-sectional study showed a correlation between DHEA-S and verbal fluency in women [39], whereas the two longitudinal studies, showed no improvement on categorization or cognitive flexibility with DHEA administration [46, 47].

3.1.5. Intelligence

Intelligence is a broad and widely used concept, but so far there is no definitive concept about it. However, we can define it as the ability to identify and solve new problems and find the best possible solution, it is the outcome of the individual's intellectual skills [49], but not includes only skills and abilities, and also includes how the brain works to process the information it receives [38]. Two studies investigated the relationship between DHEA, DHEA-S and intelligence, measuring the endogenous levels of hormones [40, 48].

The first study was conducted in 25 elderly men and evaluated crystallized intelligence, which is not sensitive to aging, and fluid intelligence, which is sensitive to aging. The results showed that DHEA-S blood levels were neither correlated with crystallized intelligence nor with fluid intelligence [40]. The other study was conducted in children ($n=60$ boys and 69 girls; mean age=5 years 11 months) using the Kaufman Brief Intelligence Test and a negative correlation was found ($r = -0.121$, $P < 0.05$.) [42].

3.1.6. Perception and Visuospatial Ability

Perception is a complex and active process in which one examines and formulates a hypothesis about the present [37]. The perception can also be described as the awareness of sensory stimuli, external objects or facts of different complexity degrees [49]. Visuospatial ability is a broad construct and involves the ability to produce, record, recall and work with images and visual sensations *via* global processing [50]. Some of the specific skills involved in visuospatial ability are: visualization, spatial relationships, closing speed, closing flexibility, visual memory and spatial rummage [51].

One study was found for each of these cognitive functions. For the first function, a longitudinal study conducted among postmenopausal women ($n=6$) assessed the relationship between visual perception and DHEA after treatment with 50 mg of DHEA daily for 4 weeks. The results of the Perceptual Identification Test showed that androgen hormones were negatively correlated with perception ($r=-.28$) [44]. The second study, a cross-sectional one, explored visuospatial ability and the endogenous levels of DHEA and DHEA-S. It was conducted in older adults ($n=981$; mean age, 62.66 years) using the Relation Figural Test. Results showed no relationship between visuospatial ability and blood levels of DHEA-S or DHEA [12]

Table 1. Summary of the studies included in this review.

Autors (Year) (Type)	n	M/F	Age	Body fluid measured	Memory	Attention	Executive Functions	Visuospatial abilities and psychomotor	Perception	Intelligence	Global Cognition	Neuropsychological Assessment Instruments	Result	Methodological aspects	Ref
Chua <i>et al</i> (2014) ³⁴ (longitudinal study)	218 PMW	0/218	59,7	Blood samples							X	A comprehensive battery of 13-item neuropsychological tests.	The analyses demonstrated no significant relation between DHEAS level and cognitive function in midlife, postmenopausal women.	<ul style="list-style-type: none"> • Adults and Elderly • Set of tests • Female population 	[34]

(Table 3) contd.....

Autors (Year) (Type)	n	M/F	Age	Body fluid measured	Memory	Attention	Executive Functions	Visuospatial abilities and psychomotor	Perception	Intelligence	Global Cognition	Neuropsychological Assessment Instruments	Result	Methodological aspects	Ref
Merritt <i>et al</i> (2012)38 (longitudinal study)	48 PMW	0/48	63,5 +/- 6,85	*	x							<ul style="list-style-type: none"> • Mini Mental State Examination (MMSE) • Digit Span Forward test (Wechsler Memory Scale-Third Edition) • Digit Span Backward test (Wechsler Memory Scale-Third Edition) • Verbal Span Performance • Modified Spenberg Paradigm 	Despite this substantial change in the hormonal milieu, DHEA administration produced no beneficial effects on cognitive performance in the digit span, verbal span, or modified Sternberg paradigm tasks.	<ul style="list-style-type: none"> • Elderly • Body fluid measured wasn't cited • Set of instruments • Female population 	[38]
Fukai <i>et al</i> (2009)23 (cross-sectional study)	208 EFD	108 / 100	70 – 95 Years (M) 70 – 93 Years (W)	Blood samples							x	<ul style="list-style-type: none"> • Hasegawa Dementia Scale – Revised 	Only in men DHEA(-S) was associated with cognitive function.	<ul style="list-style-type: none"> • Elderly • Scale • Male and Female population 	[23]
Alfaro <i>et al</i> (2008)5 (cross-sectional study)	313 E	153 / 160	76,7 +/- 5,4 (M) 77,3 +/- 6,4 (W)	Blood samples	x						x	<ul style="list-style-type: none"> • Mini Mental State Examination (MMSE) 	In women, adrenal steroids showed a negative correlation with global cognition. For memory function, DHEA also correlated negatively in women. No relationships with cognition were observed in men for any of the steroids.	<ul style="list-style-type: none"> • Elderly • Screaming test • Male and Female population 	[5]
Kritz-Silverstein <i>et al</i> (2008)39 (longitudinal survey)	112 DT 113 P	110 / 115	68,7 +/- 7,9	Blood samples	x		x					<ul style="list-style-type: none"> • Category Fluency • Word List Memory • Word List Recall 	There were no differences between the DHEA and placebo groups in change over time in cognitive function ($P > .10$). DHEA supplementation has no benefit on cognitive performance in healthy older adults, and it should not be recommended for that purpose in the general population.	<ul style="list-style-type: none"> • Elderly • Set of tests • Male and Female population 	[39]
Davis <i>et al</i> (2008)32 (cross-sectional study)	295 W	0/295	55 +/- 12,8	Blood samples	x	x	x					<ul style="list-style-type: none"> • Controlled Oral Word Association Test score • Digit Span Forward test (Wechsler Memory Scale-Third Edition) • Digit Span Backward test (Wechsler Memory Scale-Third Edition) • California Verbal Learning Test Immediate • Wechsler Memory Scale-Third Edition • Stroop Color-Naming Interference Test • Trail Making Test B (TMTB) 	DHEAS term made a significant independent Positive contribution to the Controlled Oral Word Association Test score, a measure of executive function. In addition, women with a DHEAS level in the highest tertile who also had more than 12 yr of education performed better on both Digit Span Forward and Digit Span Backward tests, which are tests of simple concentration and working memory, respectively.	<ul style="list-style-type: none"> • Adults and Elderly • Set of tests • Female population 	[32]
Kędziora-Kornatowska <i>et al</i> (2007)27 (cross-sectional study)	103 EHW 25C	0/128	70,7 +/- 7,3	Blood samples							x	<ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE) 	Statistically significantly lower DHEA-S concentration was observed in patients with benign disorders of cognitive functions and depression compared with patients with correct MMSE	<ul style="list-style-type: none"> • Elderly • Screaming test • Female population 	[27]
Haren <i>et al</i> (2007)6 (cross-sectional study)	124 EHM	124/0	56,1 +/- 4,4	Blood samples							x	<ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE) • Trail-making test (TMT) 	Higher DHEAS levels were associated with higher mini-mental state examination (MMSE) score ($b = 0.098$, $p = 0.008$).	<ul style="list-style-type: none"> • Adults • Screaming test plus gold pattern test • Male population 	[6]
Goldman e Glei (2007)22 (longitudinal survey)	836 E	*	54 and older	Blood samples							x	<ul style="list-style-type: none"> Items from: • Short Portable Mental Status Questionnaire • Rey Auditory Verbal Learning Test • Digits Backward test 	In most men low levels of DHEAS are associated with poor cognitive function. There are no significant associations among women.	<ul style="list-style-type: none"> • Adults and Elderly • Set of tests • Male and Female 	[22]

(Table 3) contd.....

Autors (Year) (Type)	n	M/F	Age	Body fluid measured	Memory	Attention	Executive Functions	Visuospatial abilities and psychomotor	Perception	Intelligence	Global Cognition	Neuropsychological Assessment Instruments	Result	Methodological aspects	Ref
Arai <i>et al</i> (2006)26 (cross-sectional)	145 E	58/87	75.6 +/- 0.56	Blood samples							x	• Mini-Mental State Examination (MMSE)	The levels of DHEA e DHEA-S were not associated with MMSE.	• Elderly • Screaming test • Male and Female population	[26]
Parsons <i>et al</i> (2006)29 (longitudinal survey)	11 DT 9P	0/20 PMW	46-66 years	Blood samples							x	• California Verbal Learning Test (CVLT) • Wechsler Adult Intelligence Scale-Revised (WAIS-R) • Digit Span Forward • Digit Span Backward • Trail Making Test A and B • Golden Stroop Test • Token Test • Category Fluency • Boston Naming Test • Test of Nonverbal Intelligence-2 (TONI-2) • Judgment of Line Orientation	An increase in negative associations between DHEA(S) levels and cognition was found at completion. Increased cortisol does not explain the cognitive deficits associated with DHEA, suggesting a direct negative effect of exogenous DHEA on cognition.	• Adults and Elderly • Set of tests • Female population	[29]
Alhaj <i>et al</i> (2006)36 (longitudinal survey)	24 YM	24/0	23.6 +/- 5.1	Saliva samples	x							• Visual analogue scales (VASS)	DHEA administration led to a reduction in evening cortisol concentrations and improved VAS mood and memory. Recollection accuracy in the episodic memory test was significantly improved following DHEA administration.	• Young • Scale • Male population	[36]
Azurmendi <i>et al</i> (2005)41 (cross-sectional)	129 C	60/69	5 years 11 months mean age	Saliva samples						x		• Kaufman Brief Intelligence Test (K-BIT)	DHEA was not a good predictor for fluid intelligence and crystallized intelligence in both genders.	• Children • Set of tests • Male and Female population	[41]
Fonda <i>et al</i> (2005)9 (cross-sectional)	981 EHM	981/0	62,66 years	Blood samples	x	x		x				• Backward Digit Span test • Digit Symbol Substitution test • Figural Relations test	The direct effects of hormones on cognition are not significant when salient factors (educational attainment, health conditions and behaviors, body mass index, and depression) are considered.	• Elderly • Set of tests • Male population	[9]
Glei <i>et al</i> (2004)21 (cross-sectional)	967 E	*	54 and older	Blood and urine samples							x	• 12 items from the modified Short Portable Mental Status Questionnaire • Rey Auditory Verbal Learning Test • Digits Backward test.	Results reveal that higher levels of DHEAS are associated with better cognitive function (among women but not men)	• Adults and Elderly • Set of tests • Male and female population	[21]
Hirshman <i>et al</i> (2004)37 (longitudinal study)	6 PMW	0/6	53-68 years	Blood samples	x	x			x			• Recognition Memory test • Digit Span • Perceptual Identification • Visual Attention Vigilance	Our results demonstrated that estrogens produced a positive effect on recognition memory and perceptual identification, while androgens produced a negative effect. Androgens also produced a negative effect on visual attentional vigilance.	• Adults and Elderly • Set of tests • Female population	[37]
Nierkerk <i>et al</i> (2001)34 (longitudinal study)	46 (EM)	46/0	62-76 years	Saliva samples	x							• Word list memory • Object location memory • Choice reaction time (CRT) • Visual search	A higher morning cortisol/DHEA ratio was also associated with lower visuo-spatial memory performance. But no significant effects of DHEA treatment were observed on any of the trial outcomes.	• Adults and Elderly • Set of tests • Male population	[34]

(Table 3) cont.....

Autors (Year) (Type)	n	M/F	Age	Body fluid measured	Memory	Attention	Executive Functions	Visuospatial abilities and psychomotor	Perception	Intelligence	Global Cognition	Neuropsychological Assesment Instruments	Result	Methodological aspects	Ref
Aleman <i>et al</i> (2001)33 (cross-sectional)	25 EHM	25/0	69,1 years	Blood samples	x					x		<ul style="list-style-type: none"> • Information (WAIS) • Vocabulary (WAIS) • Benton Judgement of Line Orientation <ul style="list-style-type: none"> • Brus Reading Test • Block Design (WAIS) • Digit Symbol (WAIS) • Concept Shifting Task • Dutch version of the Rey Auditory Verbal Learning Task.	Circulating levels of DHEAS were not associated with any of the neuropsychological measures.	<ul style="list-style-type: none"> • Elderly • Set of tests • Male population 	[33]
Moffat <i>et al</i> (2000)7 (longitudinal study)	883 EHM	883/0	22-91 years	Blood samples							x	<ul style="list-style-type: none"> • Benton Visual Retention test (BVRT) • Free and Cued Selective Reminding Test • Mini-Mental State Examination (MMSE) • Blessed Information-Memory-Concentration Test • 2 tests of mental status assessing memory, visual construction and attention • Semantic and phomenic word fluency tests • Trail-Making Tests (parts A and B) 	Decline in endogenous DHEAS concentration is independent of cognitive status and cognitive decline in healthy aging men.	<ul style="list-style-type: none"> • Young, Adults and Elderly • Set of tests • Male population 	[7]
Carlson and Sherwin (1999)25 (longitudinal study)	60 E	23/37	72.1 and 73.4 years	Blood samples							x	<ul style="list-style-type: none"> • Weschler Memory Scale (WMS) • Paragraph Recall • Paired-Associates • Selective Reminding Test • WMS-Revised • Figural Memory • Visual Paired-Associates • Visual Reproduction subtests <ul style="list-style-type: none"> • Digit Span Forward and Backward • WMS-R Visual Memory Span • Category Retrieval Test 	Results failed to provide any evidence that DHEAS is protective against declarative memory decline with aging.	<ul style="list-style-type: none"> • Small population • Elderly • Set of tests • Male and Female population 	[25]
Kalmijn <i>et al</i> (1998)28 (longitudinal study)	189 E	*	67.3 +/- 5.7	Blood samples							x	<ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE) 	There was an inverse, but nonsignificant, association between DHEAS and cognitive impairment and decline.	<ul style="list-style-type: none"> • Medium population • Elderly • Screaming test • Male and Female population 	[28]
Yaffier <i>et al</i> (1998)8 (longitudinal study)	394 EHW	0/394	65 and older	Blood samples							x	<ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE) • Trails B • Digit Symbol 	DHEAS levels declined with age, as expected. There was no consistent association of DHEAS quartile or log DHEAS with any of the four outcomes, even after multivariate adjustment.	<ul style="list-style-type: none"> • Large population • Elderly • Set of tests • Female population 	[8]
Carlson and Sherwin (1998)24 (cross-sectional study)	86 E	41/55	72.19 +/- 5.6 years	Blood samples							x	<ul style="list-style-type: none"> • Paragraph Recall • Paired-Associates • Selective Reminding Test • Figural Memory • Visual Paired-Associates • Visual Reproduction subtests <ul style="list-style-type: none"> • Digit Span Forward and Backward • Category Retrieval Test 	No significant correlations were found between any of the hormones or the DHEAS/CRT ratio and scores on any of the neuropsychological tests.	<ul style="list-style-type: none"> • Small population • Elderly • Set of tests • Male and Female population 	[24]
Wolf <i>et al</i> (1998)35 (longitudinal study)	17 E	17/0	71.1 +/- 1.7 years	Blood samples	x							<ul style="list-style-type: none"> • Picture memory test • City map test • Verbal fluency 	DHEA treatment did not enhance memory	<ul style="list-style-type: none"> • Small population • Elderly • Set of tests • Male population 	[35]
Wolf <i>et al</i> (1997)40 (longitudinal study)	40 E	25/15	69.4 +/- 1.2 (M) 69.1 +/- 1.7 (W)	Blood samples	x	x	x					<ul style="list-style-type: none"> • Concentration • Picture Memory test • Stroop test • Digit Span forward and backwards • Number connecting • Auditory verbal learning test 	DHEA replacement had no strong beneficial effect on any of the measured psychological or cognitive parameters in either sex (all <i>P</i> > 0.20).	<ul style="list-style-type: none"> • Small population • Elderly • Set of tests • Male and Female population 	[40]

Legend: DP – Depressed Patients; C – Controls; PMW – Postmenopausal women; EFD – Elderly with Functional Decline; E – Elderly; M- Men; W – Women; EHW – Elderly Healthy Women; YM – Young Men; EHM – Elderly Healthy Men; P – Placebo; DT – DHEA Treatment; *unspecified.

4. DISCUSSION

To discuss the relationship between DHEA, DHEA-S and cognitive function in populations of regular development, it is important to analyze all methodologic differences observed. Methodology design will be discussed in three levels: (1) type of study (with endogenous or exogenous hormones); (2) populations characteristics; (3) instruments used.

Regarding the type of study, some studies focused on endogenous levels whereas others focused on DHEA supplementation. No other review compiled studies with endogenous levels. In this review it was observed that studies that focused on endogenous DHEA-S levels showed a positive correlation with global cognition in women and men and a positive correlation with working memory, attention and verbal fluency (executive function) in women [9, 27 - 29, 33, 39].

We speculate that the neuropsychiatric and cognitive effects of DHEA and DHEA-S are modulated by γ -aminobutyric acid-A receptor antagonistic effects, N-Methyl-D-aspartic acid and σ -receptor potentiation effects. These hormones increases regional serotonin and dopamine activity in the brain, hippocampal primed burst potentiation and cholinergic function, anti glucocorticoid activity, inhibition of production of proinflammatory factors and bioavailability of insulin-like growth factor I [17 - 20, 52, 53]. These findings can bring greater evidence for the repercussion of DHEA-S in global cognition, working memory, attention and verbal fluency verified in this review.

However, studies with DHEA replacement failed to improve such cognitive functions [35, 41, 42, 45, 47] or even worsened their performance (negatively correlated) [36, 44]. This finding corroborates other reviews about DHEA replacement. There were four previous reviews on DHEA supplementation [54 - 57]. They showed that DHEA supplementation does not affect cognition in unimpaired people. In this review, just one of the longitudinal study with DHEA supplementation showed a positive influence on memory. However, this study comprised of young male population and a 300 mg dosage for supplementation [43], whereas other studies cited in this present review and studies cited in the previous reviews focused on elderly people using a 25 mg or a 50 mg dosage. This comparison highlights the necessity of using higher doses to achieve positive effects on cognition. However, the safety of this treatment is controversial and the risk of side effects may increase at higher doses [16, 57], although it is noteworthy that the side effects associated with DHEA use are described by literature as mild [6].

The second category of analyses clarifies additional data. Studies' designs were different in many points, such as age and the number of subjects. In the only study that proved the influence of DHEA supplementation on memory [43], the population comprised of young men. DHEA and DHEA-S concentrations peak at approximately 20 years-old and decay over time [4 - 6, 9 - 12, 15]; thus, young men have higher endogenous levels of these hormones before treatment. The other studies that did not demonstrate differences in global cognition after DHEA supplementation were all conducted on with elderly people. This finding also corroborates a previously study [56] which suggested that age related changes of human DHEA metabolic pathways may contribute to the relative inefficacy of DHEA replacement therapy.

In another article [10], a cross-sectional study showed no relationship between cognition and DHEA-S in both genders. Participants' ages ranged from 22 years to 91 years and this variation might have affected the outcome because of the differences in hormone levels in the young and elderly. This factor can explain why this finding contradicts other cross-sectional studies that demonstrate a positive correlation between DHEA-S and global cognition in both gender and memory in women.

An analysis of the characteristic of the sample in articles that did not show any correlation between endogenous hormone levels and global cognition included those with a mixed population (men and women) [30 - 32].

Regarding these differences observed in these studies, it is important to discuss gender differences in the effects of DHEA and its sulfate on memory, attention and executive function. Results that showed higher influences on memory, attention and executive function were all studies constituted of elderly women. Several authors explained this difference based on the dynamics of aging and metabolism in men and women: men have a higher exposure to gonadal hormones, which may have physical, mental and emotional implications [5]. DHEA, despite being the primary pro-hormone, is still present in lower levels in women [4]. In menopause, DHEA becomes the primary source of sex hormones in women; however, at this period, DHEA levels have declined by approximately 60%. In postmenopausal women, these levels may become undetectable in several cases. Because no other significant source of those hormones is available after menopause, low DHEA levels are associated with the majority of medical problems observed in postmenopausal women. In men, DHEA levels reach only 40% between the ages of 65 years and 75 years, and men continue to receive a

nearly constant supplementation of sex hormones from the testis throughout life, which can minimize the consequences of the DHEA deficit [58 - 61]. These findings call the attention for the longer exposure and higher concentrations to these hormones in men, which may explain the differences between genders in this review.

Other methodological factors that may contribute to the discrepancy are the different assessment materials. Different tests were used to evaluate memory, for example, some of them assessing just working memory [12, 39] or immediate auditory memory [5, 40, 45, 46], visual memory [43], recognition memory [44]. Others used a set of tests to evaluate memory as a whole [41, 42, 47]. Maybe because of these methodological discrepancies, it was possible to observe the influence of DHEA-S just in women's working memory.

Even across studies that used the same test, results can be biased due to the sensitivity of the test. In category Global Cognition, six articles evaluated global cognitive function using the MMSE [5, 9, 11, 32, 33, 35], which is a screening test that may not detect mild manifestations of cognitive dysfunction. Screening tests are widely used but are less sensitive to mild impairment [21]. Of these studies, four [11, 30, 32, 35] did not demonstrate any correlation between DHEA-S and memory. It could have happened because the tests were not sensitive enough to memory dysfunctions.

CONCLUSION

The analysis of the studies' design clarified data and showed a positive correlation between DHEA-S and global cognition in women and men, and positive correlations with working memory, attention and verbal fluency in women only. Studies with DHEA supplementation did not improve cognitive functions or worsened the performance of such functions. The only study in which DHEA supplementation was successful was conducted among young men and with higher doses of DHEA (300 mg). The use of higher doses in elderly populations should be considered in future studies because of the age-related changes in DHEA metabolism. Therefore, before the use of DHEA supplementation for cognition in clinical practice, more studies are necessary to ensure the safety of the procedure.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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