Research Report

Administration of dehydroepiandrosterone (DHEA) increases serum levels of androgens and estrogens but does not enhance short-term memory in post-menopausal women

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Abstract

The current study examines the effect of administering dehydroepiandrosterone (DHEA) on short-term memory. This experiment used a double-blind placebo-controlled cross-over design to explore the effects of a four week regimen of 50 mg oral DHEA on performance on the digit span, verbal span, and modified Sternberg (Oberauer) tasks. The results demonstrate that the current regimen of drug administration significantly increases serum levels of DHEA, DHEAS, testosterone and estrone and substantially alters the patterns of correlations among the serum levels of these hormones. 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. Ancillary analyses of the relation between hormone levels and cognitive performance demonstrated a strong positive correlation between DHEA levels and performance on digit span forward/backward and verbal span forward in the placebo drug condition, but not in the DHEA condition. We interpret the juxtaposition of the null results of DHEA administration and the correlation of DHEA levels and performance in the placebo condition to indicate that the referenced correlations arise because a third variable (i.e., age) is associated with both performance and DHEA levels. Additional analyses supported this hypothesis.

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1. Introduction

The relationship between sex steroids and cognitive performance is of critical importance in our understanding of cognition and aging. Our paper investigates the effect of dehydroepiandrosterone (DHEA) administration on short-term memory performance. Various studies have demonstrated that performance on short-term memory tasks declines with age (Macpherson et al., 2002; Wechsler, 1987), while at the same time circulating DHEA levels also decline...
DHEA is an adrenal steroid that is metabolized into its primary metabolite, DHEA-S. Plasma levels of DHEA are typically only 30% of peak levels by age 70 (Labrie et al., 1997; Orentreich et al., 1996) suggesting a mechanism by which DHEA administration enhances short-term memory. Carlson et al. (1999) demonstrated that Alzheimer’s disease patients with higher DHEA-S levels had higher forward and backward digit span scores (cf., Yaffe et al., 1998). Similarly, Yamada et al. (2010) have shown 6 months of DHEA supplementation improved verbal fluency in women with mild cognitive impairment. In contrast, Parsons et al. (2006) demonstrated levels of DHEA were negatively associated with backward digit span scores. Results from several observational studies on the effects of estrogens and androgens on short-term memory are broadly consistent with the possibility that DHEA administration may enhance short-term memory (Carlson and Sherwin, 1998, 2000; Duff and Hampson, 2000; Miller et al., 2002).

Prior studies of DHEA administration demonstrate mixed results. Hirshman et al. (2003) administered 50 mg of oral DHEA to post-menopausal women and found that performance on forward and backward digit span was approximately equal in the placebo and DHEA conditions. Similarly, using the same drug regimen and tasks Hirshman et al. (2004a) found no difference in performance across DHEA and placebo conditions. Moreover, regression analyses showed no relation between serum levels of sex steroids and performance on the digit span tasks in either the DHEA or placebo conditions. However, Wolf et al. (1997) provided evidence that administration of 50 mg of oral DHEA does enhance picture recall. Given that picture recall may be influenced by short-term visual-spatial memory, this result raises the possibility that DHEA may enhance other forms of short-term memory, even if it does not enhance digit span performance. Stangl et al., (2011) demonstrated that administration of 50 mg of DHEA had a substantial, beneficial effect on performance in a variety of visual-spatial tasks, and Yamada et al. (2010) have found significant cognitive improvements on verbal fluency following 6 months of DHEA supplementation in women with mild cognitive impairment. The possibility that short-term memory processes mediate these positive effects motivates further exploration of the effects of DHEA supplementation on tasks measuring short-term memory.

Given prior results from our laboratory and conflicting observational studies and animal studies of the effects of DHEA on short-term memory, our study sought to clarify if DHEA administration enhanced short-term memory in
post-menopausal women. We focus on this group in order to assess the effects of DHEA in a sample with relatively low endogenous DHEA levels. We used a digit span task to ensure comparability to our prior studies (Hirshman et al., 2004b; Merritt et al., 2010). Given prior results demonstrating effects on verbal tasks (e.g., Phillips and Sherwin, 1992, Yamada et al., 2010) we also included a verbal span measure. Our third task was the modified Sternberg paradigm (Oberauer, 2001). While there are no studies that have explored the effects on sex steroids on this task, we include this task because it uses verbal material and, analogous to many of the tasks used above (e.g., use of unfamiliar material in Krug et al., 2006), requires more complex short-term/working memory processing than the verbal span task. Our study is unique in that we are simultaneously testing a variety of short-term memory processes to thoroughly examine the potential for DHEA to influence short-term memory processes. The use of these three tasks will allow us to determine whether DHEA administration produces effects on any of a number of short-term memory processes.

Finally, given that potential effects of DHEA might arise from the effects of its metabolites, the time of cognitive testing is critical. Our prior work (Hirshman et al., 2004a) demonstrated that serum levels of DHEA and its metabolites peaked at approximately 10 am and maintained this level for approximately 2 hours when 50 mg of DHEA was administered orally at approximately 8 am. We selected this particular dose of DHEA given that at this dosage DHEA levels and hormone metabolites are significantly increased (Hirshman et al., 2004a) and has been shown to influence cognition (Stangl et al., 2011) while at the same time is a safe dose for our participant sample. Given this finding, all cognitive testing was conducted between 10 am and noon in the current study to ensure that we were testing at the maximal levels of DHEA and its metabolites.

2. Results

2.1. Demographic data

Participants were aged (M = 63.5, SD = 6.85), performed well on the Mini-Mental Status Exam (M = 27.77, SD = 2.42) and did not have extreme Body Mass Indices (M = 27.46, SD = 4.36). As indicated in Table 1, baseline hormone levels at the pre-enrollment evaluation were in the normal range for post-menopausal women.

Table 1: Circulating levels of DHEA, DHEAS, testosterone, estrone and cortisol (means with standard deviations in parentheses).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>DHEA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA (ng/dL)*</td>
<td>103.63 (74.23)</td>
<td>434.00 (660.31)</td>
<td>91.23 (72.82)</td>
</tr>
<tr>
<td>DHEAS (ug/dL)</td>
<td>52.15 (34.50)</td>
<td>269.19 (135.65)</td>
<td>44.39 (30.83)</td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td>18.53 (13.26)</td>
<td>51.89 (52.28)</td>
<td>15.79 (10.56)</td>
</tr>
<tr>
<td>Estrone (pg/dL)</td>
<td>20.83 (14.64)</td>
<td>31.59 (16.96)</td>
<td>18.70 (12.56)</td>
</tr>
<tr>
<td>Cortisol (ug/dL)</td>
<td>10.18 (3.67)</td>
<td>10.46 (3.66)</td>
<td>10.35 (3.36)</td>
</tr>
</tbody>
</table>

* There was 1 participant whose DHEA levels were very high. Because results did not significantly change when the participant was excluded, the participant was left in the analyses.

2.2. Circulating levels of steroid hormones

Table 1 represents circulating levels of DHEA, DHEAS, testosterone, estrone and cortisol as a function of Type of Drug (DHEA vs. Placebo). Baseline values are also included for comparison. A paired samples t-test was conducted to determine that DHEA administration was effective as indicated by the substantially higher levels of circulating DHEA; t(47) = 3.53, p < .001. The results with DHEAS, testosterone and estrone provide support that DHEA was metabolized into these related hormones (t(47) = 11.07, p < .001, t(47) = 5.41, p < .001, and t(47) = 5.06, p < .001, respectively). Levels of cortisol did not differ significantly across the conditions (p > .05).

Table 2 represents the correlations (Pearson’s) between hormones in the DHEA and placebo conditions. In the placebo condition, there were generally positive correlations among all the hormones, with many of these correlations attaining the traditional criterion for significance. The strongest of these positive correlations is between DHEA and DHEAS.

In contrast, within the DHEA condition, the correlation between DHEA and DHEAS is more moderate and there are substantially larger correlations between testosterone and DHEA/DHEAS, between estrone and DHEA and between estrone and testosterone. The changes in correlations in the DHEA condition reflect the concurrent increase in DHEA and its direct metabolites (estrone, testosterone) due to DHEA administration (see Table 1). In the case of cortisol, the observed correlation between cortisol and the other hormones in the placebo condition may arise from general health factors (e.g., the correlation of DHEA and cortisol may be due to differences in general levels of adrenal functioning across participants). In these circumstances, the substantial increases in DHEA, testosterone and estrone in the DHEA condition are not accompanied by similar increases in cortisol in the DHEA condition (see Table 1).

2.3. Affective measures

A paired samples t-test revealed that the Beck Depression Inventory (BDI) scores were not significantly different [t(47) = 1.31, p = .19, d = .19] between the DHEA condition (M = 3.58, SD = 4.19) and the placebo condition (M = 4.21, SD = 5.26). The Symptoms Checklist 90 (SCL-90) also did not differ between the DHEA condition and the placebo condition (p’s > .10) on all nine symptoms (Somatization, Obsessive...
Compulsive, Interpersonal Sensitivity, Anxiety, Depression, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism).

2.4. Digit span performance

Mean performance on the digit span task (proportion correct) as a function of Type of Drug (DHEA vs. placebo) and Type of Span (forward vs. backward) is presented in Table 3. A $2 \times 2$ (Drug x Span) repeated measures ANOVA was conducted in which the central finding is DHEA administration had no detectable effect on performance. However, there was an effect of the type of span [$F(1,47)=160.17$, $p<.001$, $\eta^2_{\text{partial}}=.77$], with forward digit span having a higher proportion correct than backward digit span. There was also no interaction between Type of Drug and Type of Span ($F<1$).

2.5. Verbal span performance

Table 3 also presents mean performance on the verbal span task (proportion correct) as a function of Type of Drug (DHEA vs. Placebo) and Type of Span (forward vs. backward). Given relatively low performance, we also used a secondary measure, proportion correct for lists of 5 or fewer words, to enhance our opportunity to detect effects of DHEA administration. We conducted separate $2 \times 2$ (Drug x Span) repeated measures ANOVAs for both verbal span measures. On both measures DHEA administration had no detectible effect on proportion correct in either the forward or the backward tasks using either measure ($F's<1$). There were also no significant effects of Type of Span or interactions between Type of Drug and Type of Span ($F's<1$). For both the regular and truncated measures. The null effects of DHEA administration were further confirmed using non-parametric analysis ($p's>.50$).

2.6. Modified Sternberg paradigm

Table 4 presents proportion correct and mean RT in the modified Sternberg paradigm as a function of length of word list (1 word vs. 3 words), stimulus type (positive, negative, intrusion) and drug condition (DHEA vs. Placebo). Proportion correct scores and mean RTs were submitted to separate $2 \times 2 \times 3$ (Drug x List Length x Stimulus Type) repeated measures ANOVAs. DHEA administration had no detectable effect on proportion correct or mean reaction time in the modified Sternberg paradigm ($F's<1$) in these analyses. There was a significant effect of stimulus type [$F(2,94)=522.92$, $p<.001$, $\eta^2_{\text{partial}}=.92$] on proportion correct. Consistent with past results (Oberauer, 2001), pairwise comparisons revealed accuracy was approximately equal for positive and negative stimuli, but was significantly lower for intrusion stimuli.

A significant effect of list length was found for RTs [$F(1,47)=350.65$, $p<.001$, $\eta^2_{\text{partial}}=.88$] with items from the 1 word list judged faster than items from the 3 word list. There was also an effect of stimulus type on reaction time [$F(2,94)=671.42$, $p<.001$, $\eta^2_{\text{partial}}=.93$] in which participants responded more slowly to intrusion stimuli than to negative
stimuli which were, in turn, responded to more slowly than positive stimuli. Finally, there was an interaction between length of word list and stimulus type \( F(2,94) = 15.99, p < .001, \eta^2_{\text{partial}} = .25 \) in which the difference in reaction time between intrusion stimuli and the positive/negative stimuli was larger in the 3 word lists than in the 1 word lists.

3. Discussion

The main purpose of this study was to examine how DHEA and its metabolites influence short term memory performance. DHEA administration was effective in manipulating hormone levels (Table 1). This supports past research showing that DHEA is an effective way to enhance circulating sex steroid levels (Morales et al., 1994,1998; Wolf et al., 1997). Because DHEA is metabolized first into androgens, followed by aromatization of estrogens (Barrou et al., 1997), the relative effects of DHEA administration on androgens and estrogens merit comment. Examining the circulating levels of each sex steroid, we notice substantial increases in DHEA, DHEA-S and testosterone. Estrone, although significantly different between drug conditions, did not increase as dramatically (see Table 1).

3.1. Prior results on short-term memory tasks

The results from our short-term memory tasks replicate multiple findings from the prior literature. Backward digit span was more difficult for our participants than forward digit span (see Table 3). Similarly, performance in the modified Sternberg paradigm demonstrated that, as in Oberauer's (2001) study, accuracy and latency were poorer for intrusion stimuli. Along the same lines, accuracy and latency were poorer on three word lists than on one word lists. In contrast to previous findings, performance on our verbal span forward task and verbal span backward task was approximately equal (see Table 3). This raises an important caution in considering the results on this task and we return to this issue shortly.

3.2. Results of DHEA administration

There were no significant differences between drug conditions on any of our short-term memory tests. Given the above evidence for the efficacy and metabolism of DHEA administration and the replication of traditional findings in digit span and the modified Sternberg paradigm, these results raise significant questions regarding whether DHEA administration enhances short term memory processes. We have cautions regarding this conclusion on the verbal span task. As mentioned above, the failure to replicate traditional findings on this task raises important questions. For example, given the relatively low level of performance on the verbal span task, this may have impaired our ability to detect effects of DHEA administration on this task.

Further, given the differences in androgenic and estrogenic metabolism cited above, the current results do not necessarily imply that estrogen do not play an important role in verbal short-term memory. Rather, it is possible that, due to the secondary aromatization of estrogens from androgens, the current manipulation of estrogens may not have been strong enough to influence cognitive performance. The prior literature highlighted a relationship between estrogen and short term verbal memory in women, and, based on these findings, it was hypothesized that DHEA administration might benefit our verbal memory measure. The null effect reported here may, however, reflect the limited estrogenic effects of clinically safe doses of DHEA, rather than the absence of estrogenic effects on verbal short-term memory tasks.

Importantly, our correlational findings in digit span and verbal span demonstrated that DHEA levels can be correlated with cognitive performance in a placebo condition (see Tables 5 and 6), even though administration of DHEA does not enhance cognitive performance in the experimental condition. It is possible that maintaining higher levels of DHEA throughout the aging process may be tied to cognition. While this result has been demonstrated across observational and experimental studies (Yanase et al., 2006; Carlson et al., 1999), this is, as far as we are aware, the first demonstration of this complex pattern in a single study.

Table 4 – Modified Sternberg paradigm accuracy means and standard deviations in parentheses for three types of stimuli (positive, negative, intrusion).

<table>
<thead>
<tr>
<th>Measure</th>
<th>DHEA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 word stimulus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (Accuracy)</td>
<td>.97 (.017)</td>
<td>.96 (.016)</td>
</tr>
<tr>
<td>Negative</td>
<td>.95 (.022)</td>
<td>.95 (.013)</td>
</tr>
<tr>
<td>Intrusion</td>
<td>.92 (.019)</td>
<td>.91 (.016)</td>
</tr>
<tr>
<td>Positive (RT)</td>
<td>1065.96 (69.43)</td>
<td>1051.44 (68.40)</td>
</tr>
<tr>
<td>Negative</td>
<td>1130.92 (79.33)</td>
<td>1114.50 (66.03)</td>
</tr>
<tr>
<td>Intrusion</td>
<td>1387.40 (107.96)</td>
<td>1390.13 (123.48)</td>
</tr>
<tr>
<td>3 words stimulus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (Accuracy)</td>
<td>.96 (.017)</td>
<td>.95 (.016)</td>
</tr>
<tr>
<td>Negative</td>
<td>.96 (.018)</td>
<td>.95 (.019)</td>
</tr>
<tr>
<td>Intrusion</td>
<td>.91 (.022)</td>
<td>.90 (.019)</td>
</tr>
<tr>
<td>Positive (RT)</td>
<td>1224.48 (82.58)</td>
<td>1215.26 (78.04)</td>
</tr>
<tr>
<td>Negative</td>
<td>1303.40 (86.77)</td>
<td>1320.34 (85.09)</td>
</tr>
<tr>
<td>Intrusion</td>
<td>1606.64 (81.83)</td>
<td>1627.51 (99.33)</td>
</tr>
</tbody>
</table>
Thus, despite substantially increasing levels of a range of sex steroids, and observing correlations between hormones and cognitive performance in the placebo condition, we were not able to find evidence that DHEA administration enhances performance on digit span, verbal span or the modified Sternberg task. These results raise significant questions regarding whether DHEA administration enhances short-term memory processes in post-menopausal women.

4. Experimental procedure

4.1. Participants

We examined 48 volunteer women 55–80 years old (M=63.50, SD=6.85) recruited by newspaper advertisement who were paid $300.00 for their participation. Participants met the World Health Organization’s criterion for post-menopausal status of one year’s absence of menses or bilateral ovariectomy that preceded the study by at least one year. No participant was using any form of hormone replacement therapy.

Participants were excluded if a pre-enrollment medical evaluation revealed contraindications to DHEA, estrogen or androgen treatment (i.e., personal history of, or active, breast cancer or other estrogen-dependent neoplasms, acute liver disease, undiagnosed vaginal bleeding, uncontrolled hypertension, deep venous thrombosis, pulmonary embolus, history of clotting disorders, history of psychiatric or cognitive disorders). Women whose pre-enrollment assays of DHEAS, estradiol or testosterone were above the normal post-menopausal women’s range or whose body mass index (BMI) exceeded 35 were excluded. Our final sample included women with BMIs from 19 to 35 (M=27.46, SD=4.36). Use of substances that influence cognition (e.g., amphetamines, benzodiazepines, narcotics, nicotine, steroid hormones, and steroid receptor antagonists) was also grounds for exclusion, as was a serious physical illness within the last year. All women enrolled had a normal mammogram within the prior year and a normal Pap smear within the prior three years.

4.2. Apparatus and design

Tests were presented on a Dell Latitude D820 laptop computer (2006). All tasks were created using E Prime (2004). Type of Drug (DHEA vs. Placebo) was manipulated using a within subject crossover design. Participants received DHEA for one 4-week period and placebo for the other 4-week period with a 1-week “washout” period between treatments. Order of treatments was counterbalanced across participants.
We administered 50 mg of oral DHEA daily. DHEA was compounded by Belmar Pharmaceutical (Lakewood, CO), the source of DHEA for numerous clinical trials. Placebos consisted of lactose and were identical in appearance to DHEA capsules. The number of pills dispensed was greater than the number needed for purposes of retrospective verification of compliance.

4.3. Measures of sex steroids

Serum levels of DHEA, DHEAS, estrone, testosterone and cortisol were measured at each cognitive testing time. Each appointment required .25 mL of serum. Samples were collected in red top tubes without a serum separator. Blood was allowed to clot for 20 min. Afterward the blood samples were placed in a centrifuge at 4000 rpm for 5 min. The serum was then separated and frozen at −80°C. Assays were all conducted on site at the General Clinical Research Center of Georgetown University Medical Center by Dr. Soldin’s laboratory. Researchers at Georgetown University (Guo et al., 2004) had recently developed a variant of liquid chromatography tandem mass spectrometry relying on stable isotope dilution to measure steroid hormone levels. These methods have the significant advantage of providing rapid simultaneous quantitation of multiple steroids in a single blood sample.

4.4. Procedure

Participants who responded to newspaper advertisements underwent a 5-minute telephone interview. Individuals who met the entry criteria were set up for a pre-enrollment evaluation at the General Clinical Research Center at Georgetown University Hospital. The evaluation began with informed consent. If the participant agreed to participate in the study a history, including review of illnesses, medications, and contraindications to steroid hormone administration was taken. A physical exam was performed and blood was drawn for a complete blood count (CBC), CHEM 7 (including electrolytes, blood urea nitrogen and creatinine), as well as baseline sex steroid assays (DHEA, DHEAS, testosterone, estrone and cortisol). The Symptom Checklist 90-R (SCL 90-R) (Derogatis and Savitz, 2000) and the Mini-Mental Status Exam (Turvey et al., 2000) were administered.

Participants were assigned to receive DHEA or placebo in a block-randomization scheme. All investigators and participants were blind to treatment status. Upon receipt of the appropriate pillbox, participants were instructed to take one pill each morning with breakfast and to write any significant adverse events on a provided diary sheet.

Cognitive testing occurred in 28 days and participants were instructed to fast after midnight and to not consume any caffeine. At 7:30 am the participant was expected to arrive and given breakfast. At 8:00 am the participant ingested either 50 mg of DHEA or placebo. A blood draw was performed at 9:50 am. Cognitive testing occurred between 10 am and noon on each testing day. We chose this specific time because steroid levels are maximized during this period in the DHEA condition (Hirshman et al., 2004a). Each cognitive task was presented once during each testing session. At 12:30 pm, the Beck Depression Inventory and the SCL-90 tests were administered.

At the end of the first test day, participants were given appropriate pills, an appointment for the second testing session, and new diary sheets. Participants were instructed to begin taking the pills in one week and a reminder call was made prior to the second testing day. Testing procedures were identical on the second test day, except participants were debriefed at the end of this day.

4.5. Cognitive measures

We tested participants on cognitive tasks designed to measure the elementary processes influencing short term memory. Order of task presentation was randomized across participants.

4.5.1. Digit span

Participants were presented with a list of digits ranging from 2 to 10 in a random sequence. After presentation, participants were asked to repeat the digits in the order presented or “forwards” condition. There was also a “backwards” condition in which participants were asked to repeat the digits backwards from the original sequence. The order of these 2 conditions was randomized and there were a total of 45 trials in each condition. The proportion of trials out of 45 trials on which the participant correctly recalled the presented sequence was the participant’s score.

4.5.2. Verbal span

On each trial, participants were presented with a series of words in a random sequence ranging from 2 to 10 words. A counting task then occurred in which the participant must count backwards from whatever number is presented for a period of 15 s. Following this, the participant must write down the words they were presented in the same order, or “forwards” condition. Participants were also asked to write down the words in a “backwards” condition from the original sequence. The order of these conditions was randomized and there were a total of 45 trials in each condition. The proportion of trials out of 45 trials on which the participant correctly recalled the presented sequence was the participant’s score.

4.5.3. Modified Sternberg paradigm (Oberauer serial scanning)

Two lists of items were presented on the computer monitor to the participant (lists contained 1 and 3 words). The word list at the top of the screen was presented in blue ink and the list at the bottom was in red ink. The presentation time for the lists was 1.3 s times the total # of words in the 2 lists. The participant was cued to which list was the target list by a rectangular frame in the middle of the screen in the color of the list the participant should remember. After a 600 ms cue-stimulus interval, the test item was presented. This item was presented in the color of the target list. The participant’s task was to judge if the test item was from the target list or not. Participants were presented with 80 trials. Fifty percent of the tested items were from the target list, 25% of the tested items were from the other presented list (intrusion), and 25% of the tested items had not been presented on either list

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(negative). The proportion of correctly identified test words and the latency of response were measured.

4.6. **Affective measures**

4.6.1. **Modified Mini-Mental Status Exam**
During the pre-enrollment period, participants were given the Mini-Mental Status Exam (Turvey et al., 2000). This consisted of 11 questions with a total possible score out of 30.

4.6.2. **Beck Depression Inventory**
The Beck Depression Inventory (Steer et al., 1999) was used to measure whether DHEA affected depression. This self-report inventory consists of 21 questions examining a participant’s hedonic state and physiological functioning. Scores less than 10 do not generally motivate clinical inquiries.

4.6.3. **Symptom Checklist 90-R**
The Symptom Checklist 90-R (SCL 90-R) (Derogatis and Savitz, 2000) was administered during the pre-enrollment period, Test Day 1 and Test Day 2. It consisted of 90 questions about physical and mental ailments that may have bothered them in the past week including that day. The test was then scored in 9 different scales for somatization, obsessive compulsive, interpersonal sensitivity, anxiety, depression, hostility, phobic anxiety, paranoid ideation, and psychoticism.

4.7. **Hormone variables**
Serum levels of DHEA, DHEAS, testosterone, estrone and cortisol were also measured.

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