Dehydroepiandrosterone Sulfate Levels Are Associated with More Favorable Cognitive Function in Women

Susan R. Davis, Sonal M. Shah, Dean P. McKenzie, Jayashri Kulkarni, Sonia L. Davison, and Robin J. Bell

Women's Health Program (S.R.D., S.M.S., S.L.D., R.J.B.), Department of Medicine, Monash Medical School, Alfred Hospital, Prahran, Victoria 3181, Australia; and School of Psychology, Psychiatry and Psychological Medicine (S.M.S., J.K.) and Department of Epidemiology and Preventive Medicine (D.P.M.), Monash University, Prahran, Victoria 3181, Australia

Context: It has been proposed that dehydroepiandrosterone and dehydroepiandrosterone sulfate (DHEAS) exert neuroprotective effects in the brain, yet evidence of associations between the endogenous levels of these steroids and measures of cognitive function is lacking.

Objective: The objective of the study was to investigate whether circulating levels of DHEAS independently contribute to aspects of cognitive function in women in the community.

Design: This was a community-based, cross-sectional study.

Setting and Participants: Two hundred ninety-five women, aged 21–77 yr, were recruited from a community-based data set and participated between September 2003 and December 2004. Women were excluded if they reported any health condition that might potentially adversely affect cognitive function.

Main Outcome Measures: The individual scores of a comprehensive battery of tests of cognitive function and the serum level of DHEAS (square root transformed) were measured.

Results: In the multiple linear regression analysis, the 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.

Conclusions: Higher endogenous DHEAS levels are independently and favorably associated with executive function, concentration, and working memory. **(*J Clin Endocrinol Metab* 93: 801–808, 2008)**

Dehydroepiandrosterone (DHEA) and its sulfate DHEAS, which serves as the principal circulating storage form of DHEA, are primarily products of the adrenal cortex. These steroids are the most abundant circulating sex steroids in women, providing a large precursor reservoir for the intracellular production of androgens and estrogens in nonreproductive tissues (1). Furthermore, these steroids are synthesized within the brain (2) and appear to have central effects that are independent of estrogen or androgen receptors (3). There are data that suggest DHEA and DHEAS may have neuroprotective effects and that the decline in the production of these steroids with healthy aging (4) may contribute to neuronal dysfunction and degeneration and thus cognitive decline (3).

Evidence that endogenous levels of DHEA and DHEAS are associated with more favorable cognitive function during healthy adult life is lacking. Large studies in men do not show an

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2007-2128 Received September 21, 2007. Accepted November 29, 2007.

First Published Online December 11, 2007

Abbreviations: $\sqrt{}$, Square root transformed; CART, Classification and Regression Tree; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DSB, digit span backward; DSF, digit span forward; FAS, Controlled Oral Word Association Test; Stroop, Stroop Color-Naming Interference Test; TMTB, trial making test B; VR, verbal recall.

association between endogenous DHEA/DHEAS and cognition (5, 6). However, Moffat *et al.* (5) administered only a single test of cognition to men under the age of 60 yr, and Fonda *et al.* (6) limited their study to men aged 48–80 yr. Furthermore, androgen physiology differs substantially between women and men such that the adrenal preandrogens, DHEA and DHEAS, become the major source of both estrogen and testosterone production in women once ovarian function ceases at menopause.

The aim of this study was to establish the relationships between circulating DHEAS, a robust measure of DHEA production (2, 7), and several measures of cognitive function in a community sample of women initially recruited from the community for the study of Endogenous Androgen Levels in Women across the Adult Life Span (4), taking into account relevant demographic and lifestyle factors.

Subjects and Methods

The study sample

Between April 2002 and August 2003, 1423 women, aged 18–75 yr, were recruited across Victoria, a southeastern state of Australia, to the community-based, cross-sectional study, Endogenous Androgen Levels in Women across the Adult Life Span (4). This sample population was drawn from the Victorian section of a database that was a robust, nationally representative sample of the Australian population as previously described (8). In brief, a database of eligible women was created using the following methodology: women were recruited by telephone using a database of individuals from household addresses selected at random on a weekly basis from Australian electoral areas. In Australia because voting is compulsory, every adult must be registered on the electoral roll. Each electoral area was divided into sampling points of approximately equal numbers of 25,000 each. Melbourne had 105 sampling points, and country Victoria had 43 sampling points. Starting addresses were selected at random from the electoral roll for each of the sampling points. Interviews were conducted in person on Saturdays and Sundays between 0900 and 1600 h. Eight interviews were conducted per sampling point. Only one eligible person was recruited per household, and people recruited to the sample tend to stay on the active database for about 2 yr. For this study the database as of May 2002 was used initially, with eventual inclusion of past members of the database, back to 1998, to recruit sufficient women to the study. Women from the database underwent telephone screening. Women were excluded if they were pregnant or less than 6 wk postpartum or had experienced any of the following in the preceding 3 months: an acute psychiatric illness; acute renal, liver, or cardiovascular disease or any other acute major illness; gynecological surgery; active malignancy or cancer treatment, excluding nonmelanotic skin cancer.

Women were eligible for this substudy of cognitive function if they had been participants in the aforementioned study and were agreeable to being recontacted about participation in further studies and if on further screening they did not report any of the following: alcohol consumption greater than three standard drinks a day; a history of brain tumor; significant past head injury; any strokes or ministrokes; brain tissue disease; ongoing epilepsy; Alzheimer's disease or any dementia; Parkinson's disease; pituitary tumor with radiotherapy; hospitalization (lifetime) for depression or major psychiatric illness; an episode of major depression (according to the *Diagnostic and Statistical Manual of Mental Disorders IV* classification); or current use of a prescription drug for depression or a prior diagnosis of cancer.

This study was approved by the Standing Human Research and Ethics Committee, Monash University, Australia, and all participants provided written informed consent.

Participant assessment

Women living or working in the metropolitan area were given the option of two different clinical assessment sites. Women living outside the Melbourne metropolitan area were seen at one of nine major regional centers in rural Victoria. Participants read and signed the information and consent form at the beginning of their visit. Weight (kilograms) in light clothing and without shoes and height (meters) were recorded and body mass index was calculated. All assessments were undertaken by a single researcher (S.M.S.) between September 2003 and December 2004, and all evaluations were performed in a set order. Participants provided details regarding their education level, marital status, living arrangements, work outside the home, exercise, leisure activities, smoking, alcohol intake, use of the oral contraceptive pill or hormone therapy, and other medications.

Menopausal status was established using a decision tree based on the answers to a series of questions that included age, history of bilateral oophorectomy or hysterectomy, whether she reported regular menstrual bleeding or if she reported that her periods had ceased, and how many months had passed from the last period. We also asked about vasomotor symptoms.

Measurement of cognitive function

Each participant underwent a battery of tests known to measure a wide range of cognitive abilities including verbal, visual, spatial and working memory, attention and concentration, speed, and accuracy. The tests were always administered in fixed order.

The California Verbal Learning Test Immediate (9) is a test of verbal learning and retention that involves presentation and subsequent free recall of a list of 16 words comprising four kinds of shopping items. The visual reproduction subtest of the Wechsler Memory Scale-Third Edition (10) is a test of nonverbal memory and retention that involves presentation of a simple geometric diagram for 10 sec, which the participant is then required to draw from memory (VR immediate). The designs are drawn from memory again after a 30-min delay (VR delayed). The Controlled Oral Word Association Test (FAS) (11) is a test of executive function that measures initiation of verbal ideation and mental flexibility. The Stroop Color-Naming Interference Test (12) (Stroop) provides a measure of focused attention and inhibition of interfering dominant responses. Trail Making Test B (TMTB) (13) assesses executive functioning. The digit span subtest of the Wechsler Memory Scale-Third Edition (10) provides a test of simple concentration [digits forward (DSF)] and working memory, which captures the ability to hold information in mind while working on a problem [digits backward (DSB)].

Hormone measurement

Fasting blood was drawn at the time of recruitment to the study of Endogenous Androgen Levels in Women across the Adult Life Span (4), which was on average 1.70 yr (SD 0.37 yr) before the cognitive assessments. Sera were stored at −80 C until assayed. DHEAS was measured by a solid-phase, two-site chemiluminescent enzyme immunometric assay using the Immulite automated analyzer (Diagnostic Products Corp., Los Angeles, CA). The intraassay coefficient of variation is 6.8–9.5% and the interassay coefficient of variation is 9.2–12.7%.

Physical and leisure activity

Physical exercise was assessed using a number of questions developed specifically for this study, which have not been validated. Women were classified as participating in vigorous exercise if they responded "yes" to a question about vigorous recreational exercise (such as jogging, cycling, or competition tennis) or strenuous gardening or yard work. Given that the median age of the women in the study was 55 yr and that gardening is a popular recreational activity of older women in Victoria, it was important that strenuous gardening was included within this variable.

Sample size

The sample size calculation was based on the proposal to model the determination of cognitive function using linear regression. With a value

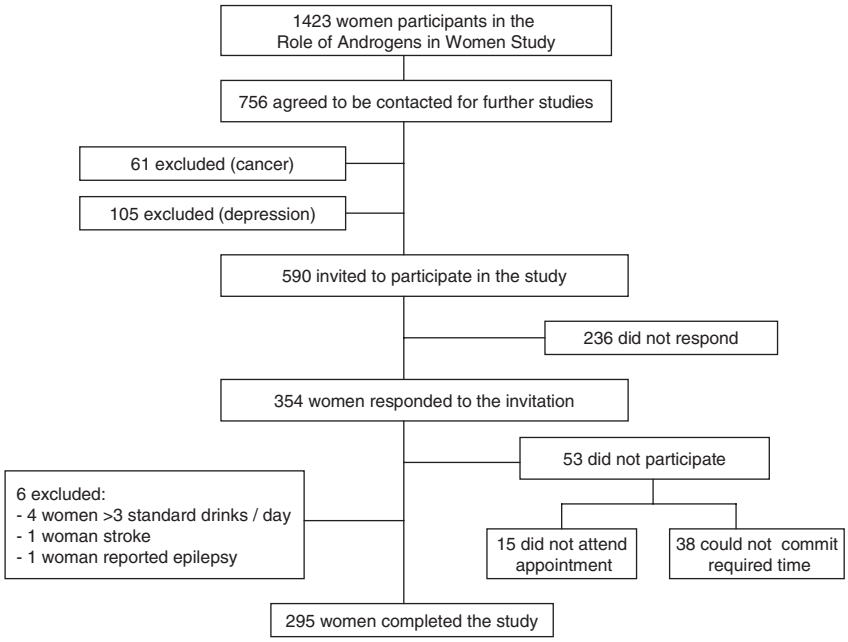

FIG. 1. Recruitment of study participants.

for r of 0.25, $r^2 = 0.067$ (the model would explain 6.7% of the variation in the dependent variable), recruitment of 300 women in the study would have provided a power of greater than 90% (14).

Statistical analysis

Because the data describing serum DHEAS were not normally distributed, these were square root transformed ($\sqrt{}$) to improve the normality of their distributions (15). Many of the independent variables were dichotomized.

The approach taken to the analysis was to set up a standard model against which to regress each of the cognitive outcomes. The decision about which variables to include in the standard model was based on a number of considerations including the results of univariate analyses between each variable and each cognitive outcome; the need to include some variables that, although not achieving statistical significance in the univariate analysis, their inclusion was considered important to minimize confounding (*i.e.* age was included in the standard model so that the effects of variables such as menopause status or androgen levels were not confounded by age effects); and finally the issue of multicollinearity (16). There were a number of situations in which it was inappropriate to include groups of variables because they were highly correlated with each other. An example is that virtually all women who reported being married or in a *de facto* relationship also reported living with other people, so the inclusion of both of these variables was problematic. Because there were women living with others who were not partnered, we decided to include living with others rather than marital status in the analysis as a measure of the social setting in which women lived.

A standard model was developed that included the following 13 variables: age (continuous), body mass index (continuous), systemic estrogen treatment (dichotomous), menopause status (dichotomous), smoking (dichotomous), alcohol consumption (dichotomous), doing crossword puzzles (dichotomous), playing a musical instrument (dichotomous), doing regular vigorous exercise (dichotomous), educated beyond year 12 at school (dichotomous), being employed outside the home (dichotomous), living with others (dichotomous), and blood DHEAS (square root transformed, continuous). This model was then regressed against each of the cognitive outcomes. The variables within the standard model in which the regression coefficient was statistically significantly different from zero were further examined in a reduced model for each cognitive outcome to determine the contribution of the subset of significant variables to each outcome. Age was frequently identified as a significant main effect. Where it was not identified as a main effect that was statistically significant at the 5% level in the standard model, we forced it into the reduced model to avoid other main affects being falsely identified because they were confounded by age (this is particularly important for variables such as menopausal status, $\sqrt{}$DHEAS, and working outside the home).

Linear regression modeling was carried out using the statistical package SPSS (version 14.0.2; SPSS Inc., Chicago, IL). The statistical significance of each variable is given by the *P* value for the test of whether the coefficient of the variable is different from zero. The sign (+ve or −ve) of the regression coefficient of an independent variable indicates the direction of the relationship between that independent variable and the dependent variable. The r^2 value for each model indicates the overall proportion of the variation in the cognitive measure that is explained by the model (16).

To investigate potential interactions among the independent variables, we used a computer-based technique known as recursive partitioning. This technique has been recommended for identifying interactions, including nonlinear ones, in epidemiological data (17, 18) and attempts to reduce the possibility of finding spurious relationships. Recursive partitioning looks for interactions by using a tree structure to recursively subdivide or partition the data set into subgroups that are homogeneous in regard to the dependent variable (19). Relationships that hold for some subgroups (*e.g.* for particular age groups), but not others, can then be identified. We used the Classification and Regression Tree (CART) algorithm (19, 20), which attempts a trade-off between model cost or performance and model complexity (the number of subgroups in the tree). CART has been empirically shown to be highly conservative in constructing tree models and has recently been applied to endocrinological and other data (17, 21, 22). Separately CART was used to assess whether there were any statistically significant interactions between variables in the standard model in relation to each outcome. This process was independent of the linear regression modeling and may have identified interactions involving variables that had not been chosen as important main effects in the standard model. The impact of adding the identified possible interaction to the each of the reduced models was then statistically assessed. Care should always be exercised in interpreting statistical models, particularly in smaller samples. The true test of a main effect or interaction is whether it can be replicated in another sample; however, CART has the added advantage of developing models through cross-validation (creating models on facets of the data and then testing them on held-out facets of the data) rather than significance testing.

Results

Of the 756 women who agreed to be recontacted for future studies, before any attempt at recontact, 105 women were excluded because of antidepressant use and 61 because of a history of cancer. Of the 354 who responded (from the 590 recontacted), 53 did not participate: 38 had other commitments such as work and 15 did not attend their appointment. In addition, six women were excluded on the basis of the other prespecified exclusion criteria (Fig. 1). The mean age of the 295 participants was 55.0 (SD 12.8) yr. The participants' characteristics are shown in Table 1. Compared with participants in this study, women in the original cohort were on average 5 yr younger (mean age 50.0 ± 14.4 yr), the proportion who were postmenopausal was smaller

(49.9%), their mean DHEAS level was higher (3.1 ± 2.17 μmol/liter), and their body mass index was similar (27.8 ± 6.5 kg/m^2) (4). The proportion of smokers in the original group was 15.4% and the proportion of women who drank alcohol was 68.2%. None of the participants were taking DHEA at the time of the study.

For each of the cognitive measures, we established the proportion of the variation explained by the standard model, as described above, and which of the variables in the standard model made statistically significant contributions. For each cognitive measure, a reduced model was constituted from the statistically significant variables and age. Interactions between variables in the standard model, identified using CART, were then introduced into the reduced model (Table 2).

For the FAS test, 22.5% of the variance was explained by the standard model ($r^2 = 0.225$). The reduced model for FAS contained seven variables including √DHEAS as a main effect. These seven variables alone explained 21.7% of the variation in the FAS test score (Table 2). No significant interactions for FAS were identified using CART.

The standard model for DSF explained only 9.4% of the variation in this cognitive domain ($r^2 = 0.094$). The reduced model, which included education and employment outside the home, with age forced in, explained 6.4% of the variation in DSF. CART identified an interaction between √DHEAS and education such that inclusion of the interaction terms into the reduced model significantly increased the variation in DSF explained to 10.6%, an increase that was statistically significant ($P = 0.001$). The interaction between √DHEAS and education was such that the favorable impact of increasing levels √DHEAS on the DSF score was more pronounced for women who had been educated beyond yr 12 at school (Table 3). For DSB, 7.9% of the variation was explained by the standard model. Again the reduced model contained education and employment outside the home, with age forced in. These three variables alone explained 4.2% of the variation in DSB. As for DSF, an interaction between √DHEAS and education was identified and inclusion of this into the reduced model doubled the proportion of variation in DSB explained ($r^2 = 0.089$) with an effect similar to that seen for DSF (Table 3). The increase in r^2 was statistically significant ($P = 0.004$).

The standard model explained 8.2% of the variation in the Stroop test, with more than half of this explained by the reduced model that included age, menopause status, and living with others (4.9%). An interaction among age, menopausal status, and living with others was identified by CART. When the interaction terms were included in the reduced model, the variation in Stroop increased to 11.9% ($r^2 = 0.119$), an increase that was statistically significant ($P = 0.001$). The directionality of the interaction was such that for women less than 64.5 yr of age who were postmenopausal, those who lived with other people had a more favorable score than those who lived alone.

Thirty-three percent of the variation in TMTB was explained by the standard model, the reduced model explaining 30.9% of the variation. An interaction between age and doing crossword puzzles was identified, which, when included, increased the proportion of the variation explained to 33%, this increase being slight but statistically significant ($P = 0.02$). The favorable impact of doing crossword puzzles on the TMTB score was much greater in older than younger women.

The standard models for VR immediate and VR delayed explained 30.8 and 19.4% of the variation in each of these cognitive domains, respectively. The reduced models for each of these cognitive tests included age, education, and living with others and explained 28.5 and 16.9% of the respective variation of each. No significant interactions for either VR immediate or VR delayed were identified.

For California Verbal Learning Test immediate, 18.5% of the variation was explained by the standard model and 16.7% by the reduced model, which included age, menopausal status, playing a musical instrument, and education. Again no significant interactions were identified.

TABLE 1. Participant characteristics

	Participants (n = 295)	
	Mean (SD)	**Proportion (%)**
Age (yr)	55.0 (12.8)	
Body mass index (kg/m^2)	28.1 (6.5)	
DHEAS (μM/liter)	2.95 (2.08)	
Married/*de facto*		174 of 290 (60.0)
Educated > yr 12		174 of 290 (60.0)
Employed outside the home		162 of 291 (55.7)
Lives with others		221 of 291 (75.9)
Regular vigorous exercise		172 of 291 (59.1)
Smoker		27 of 295 (9.2)
Drinks alcohol		221 of 290 (76.2)
Does crossword puzzles		145 of 291 (49.8)
Plays a musical instrument		30 of 291 (10.3)
Postmenopausal		179 of 295 (60.7)
On systemic estrogen		24 of 295 (8.1)

Discussion

This study provides the first evidence that cognitively intact women with higher circulating levels of DHEAS exhibit better performance on testing of executive function (FAS test) and that circulating DHEAS is significantly positively associated with higher scores for tests of simple concentration (DSF) and working memory (DSB) in women with at least 12 yr of education. Circulating DHEAS levels were not associated with performance on tests of verbal and nonverbal learning and retention or focused attention. The other findings of interest include the favorable independent associations between living with other people, doing crossword puzzles, playing a musical instrument, and cognitive performance. Because no single factor beyond intelligence testing is likely to account for a large proportion of variation in cognitive performance, that the models we generated explain between 8.9 and 33% of the variation in each of the cognitive tests undertaken is meaningful.

Maintenance of cognitive function in elderly women is influenced by a number of other health variables including diabetes, hypertension, and smoking (23), and longitudinal studies have reported associations between these factors and progression to

TABLE 2. Contribution of variables of interest to cognitive test score

Reduced model	β coefficient	*P* value	r^2 value for the reduced model	Reduced model + interactions	β coefficient	*P* value	r^2 value for the model	*P* value for Δ r^2
FAS								
Age	0.213	0.002						
Body mass index	−0.329	0.005						
On systemic estrogen	−5.678	0.037						
Crossword puzzles	5.615	0.000						
Plays a musical instrument	6.220	0.012						
Educated beyond yr 12	7.831	0.000						
√DHEAS	4.188	0.005						
			0.217					
DSF								
Age	0.004	0.773		Age	0.013	0.374		
Educated beyond yr 12	0.929	0.001		Educated beyond yr 12	−0.647	0.247		
Employed outside home	0.732	0.029	0.064	Employed outside home	0.718	0.029		
				√DHEAS	0.020	0.947		
				Education beyond yr 12 and √DHEAS > 0.97	1.871	0.001		
							0.106	0.001
DSB								
Age	0.026	0.096		Age	0.034	0.035		
Educated beyond yr 12	0.682	0.006		Educated beyond yr 12	−0.162	0.759		
Postmenopausal	−0.878	0.031		Post enopausal	−0.913	0.022		
			0.042	√DHEAS	−0.123	0.676		
				√DHEAS > 1.12 and education ≤ year12	0.494	0.334		
				√DHEAS > 1.12 and education beyond yr 12	1.564	0.001		
							0.089	0.004
Stroop								
Age	0.106	0.069		Age	−0.097	0.174		
Lives with others	−3.191	0.003		Lives with others	−1.729	0.176		
Postmenopausal	−3.474	0.022		Postmenopausal	4.678	0.039		
			0.049	Age ≤ 64.5 and postmenopausal and lives with others	−7.327	0.000		
				Age ≤ 64.5 and postmenopausal and does not live with others	−4.533	0.031		
							0.119	0.001
Trail making test B								
Age	0.668	0.000		Age	0.220	0.319		
Alcohol	−6.017	0.028		Alcohol	−5.770	0.034		
Crossword puzzles	−8.488	0.000		Crossword puzzles	−5.249	0.050		
Educated beyond yr 12	−6.002	0.011		Educated beyond yr 12	−5.216	0.027		
Employed outside home	−5.855	0.033		Employed outside the home	−5.211	0.069		
			0.309	Age ≤ 42.5	−14.365	0.092		
				Age > 42.5 and age ≤ 63.5	−4.491	0.356		
				Age > 63.5 and crossword puzzles = yes	10.607	0.032		
							0.333	0.02
VR immediate								
Age	−0.457	0.000						
Educated beyond yr 12	+6.409	0.000						
Lives with others	+5.019	0.006						
			0.285					
Visual reproduction delayed								
Age	−0.464	0.000						
Educated beyond yr 12	+9.552	0.000						
Lives with others	+6.411	0.031						
			0.169					
California Verbal Learning Test								
Age	−0.070	0.291						
Postmenopausal	−3.460	0.046						
Plays a musical instrument	7.702	0.000						
Educated beyond yr 12	2.681	0.012						
			0.167					

TABLE 3. Interactions between serum DHEAS and DSF and DSB test scores

	DSF test score [mean (SD)]		DSB test score [mean (SD)]	
Tertile $\sqrt{}$DHEAS	Education ≤ 12 yr	Education beyond 12 yr	Education ≤ 12 yr	Education beyond 12 yr
Lowest	9.36 (2.06)	9.78 (2.77)	6.43 (1.90)	6.48 (1.88)
Middle	9.55 (2.44)	10.81 (2.22)	6.78 (1.95)	7.44 (1.91)
Highest	9.80 (2.21)	11.02 (2.17)	6.40 (2.25)	7.60 (2.11)

dementia in elderly individuals (24, 25). Less is known of the determinants of cognitive function in younger women in the community, well before the onset of cognitive decline. In our study population, we were specifically interested in the associations between each of DHEAS, social circumstances, and leisure activities and cognitive performance.

Possible explanations for our findings include direct actions of DHEA/DHEAS via a putative DHEA receptor (26, 27), via the androgen receptor (28), or as neurosteroids and endogenous ligands for σ-1 receptors (3, 29–31) and/or DHEAS being a marker of overall potential for tissue intracrine androgen and estrogen production in women (1) but not the actual mediator of the effect (8). Alternatively, DHEAS may be simply a marker of general good health. To our knowledge, data pertaining to any relationships between circulating and cerebral DHEA/DHEAS concentrations are lacking.

Our findings differ from, but are not in conflict with, what has been reported in men (5, 6). Although DHEA and DHEAS levels decline in both men and women with age (32), testosterone levels are generally well maintained in men well into old age, being always severalfold greater than levels measured in women. In contrast testosterone levels in women decline progressively with age from the midreproductive years (4) such that small differences in adrenal preandrogen production may make a substantial difference to a woman's overall androgenic milieu.

Our findings do not provide evidence that exogenous DHEA is beneficial for cognitive function. The published randomized, controlled trials of DHEA therapy on cognitive outcomes do not support a beneficial effect of such therapy (33–36) and adequately powered studies of sufficient duration to determine whether DHEA administration is beneficial still need to be conducted (37).

That a higher level of education was significantly associated with better cognitive performance is consistent with the literature (25, 38). Similarly, having a higher occupational complexity and social engagement have been positively associated with cognitive performance in longitudinal studies (25, 39). That employment outside the home made an independent contribution to cognitive performance is a novel but not unexpected finding. Findings from a small cross-sectional study of orchestral musicians supports the notion that dementia is less common among musicians (40). Our study provides what we believe to be the first evidence that women who report playing a musical instrument exhibit better performance on tests of verbal memory, verbal ideation, and mental flexibility. Whether these characteristics are inherent in musical aptitude or a consequence of musical training or continued practice merits further exploration (41).

Individuals living alone appear to be at greater risk of developing dementia (24). We report independent associations between living with others and better performance on tests of nonverbal memory and retention and focused attention and inhibition of interference. This is new evidence that living with others has favorable effects on cognition in well individuals in the community.

That we did not identify any independent association between physical activity and any measure of cognition may be a type II error of missing an effect that is really there as a consequence of using the nonvalidated measure of physical activity.

Strengths of our study are that the participants were women recruited from the community via the electoral roll, in the context that voting in Australia is compulsory, that were of a broad age range, and that we were able to include a number of important sociodemographic variables in the analysis. The women who agreed to participate in this study of cognition were not a random selection of the original group of 1423. The participants were women who had initially agreed to be recontacted about participating in a range of future studies and then subsequently agreed to participate in this study. That only about half of those who participated in the original study agreed to be recontacted reflects the demands of that study, in that some participants living in rural areas traveled a considerable distance to a blood collection center for fasting blood to be drawn, also timed to the cycle for premenopausal women. Participation in this study was good, given that women living in rural and remote areas were again required to travel to regional centers to complete cognitive testing that took up to 1.5 h.

That the mean age of women who went on to participate in this study was greater than for the original cohort is not surprising because the younger women from the original study were clearly pressed for time in relation to further participation because of both work and family commitments. The higher proportion of postmenopausal women, lower mean DHEAS level, and lower proportions of smokers and drinkers in the cognition study is consistent with the older mean age of these participants.

Of note, DHEA is not available in Australia. Hence, there was no selection bias to nonusers of DHEA in the community. Taken together, this was not a convenience sample.

A limitation of our study was that DHEAS was measured on only one occasion. However, DHEAS is not bound to SHBG (42), the assay methodology is robust, and the main factor impacting on serum levels is age (4).

Although the blood samples collected for the DHEAS measurements for this study were collected some months before the cognitive testing, the study design is essentially cross-sectional and as such does not inform the issue of cause and effect. It just allows us to investigate associations.

However, we believe that our findings provide a strong basis for future studies designed to test the cause-and-effect nature of the relationship between serum levels of DHEAS and cognitive function in women.

In conclusion, we have identified several factors, including serum DHEAS levels, that independently contribute to cognitive performance in women in the community. It is not surprising that the differences noted in relation to cognition are subtle. We would have been surprised if they were not, considering the complexity of human cognitive function. The potential clinical significance cannot be determined from this research. It requires the robust testing of a cause-and-effect relationship and ideally a randomized trial to assess whether exogenous administration of an appropriate agent, such as DHEA, has an impact on cognitive function.

Acknowledgments

We appreciate the assistance of Roy Morgan Research Australia in the conduct of this research.

Address all correspondence and requests for reprints to: Dr. Susan Davis, M.D., Ph.D., Women's Health Program, Department of Medicine, Central and Eastern Clinical School, Monash University, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia. E-mail: susan.davis@med.monash.edu.au.

This work was supported by National Health and Medical Research Council of Australia Grant 219279. The funding agencies had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication. All coauthors had complete access to the data.

Disclosure Statement: S.R.D. has received unrestricted research grant support from Acrux Australia; has been a consultant for Acrux Ltd. and Procter & Gamble; and is an investigator for Procter & Gamble, Acrux, and Organon. J.K. has received research grant support from Eli Lilly Pharmaceuticals, Janssen-Cilaag Pharmaceuticals, and Sanofi-Synthelabo Pharmaceuticals and has received honoraria from Eli Lilly, Bristol Meyer Squibb, Janssen-Cilaag, and Sanofi-Synthelabo. R.J.B. has received unrestricted grant support for other research studies from Astra Zeneca Australia, Novartis, and Proctor & Gamble. S.L.D. has received research grant support from Acrux Ltd. The other authors do not have any disclosures to declare.

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