

Concurrent Change in Dehydroepiandrosterone Sulfate and Functional Performance in the Oldest Old: Results From the Cardiovascular Health Study All Stars Study

J. L. Sanders,^{1,2} A. R. Cappola,³ A. M. Arnold,⁴ R. M. Boudreau,² P. H. Chaves,⁵ J. Robbins,⁶
M. Cushman,^{7,8} and A. B. Newman^{2,9}

¹Medical Scientist Training Program, School of Medicine and ²Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pennsylvania.

³Department of Medicine, School of Medicine, University of Pennsylvania, Philadelphia.

⁴Department of Biostatistics, University of Washington, Seattle.

⁵Center on Aging and Health, Department of Epidemiology, School of Public Health, Johns Hopkins University, Baltimore, Maryland.

⁶Department of Internal Medicine, School of Medicine, University of California Davis, Sacramento.

⁷Department of Medicine and ⁸Department of Pathology, University of Vermont College of Medicine, Burlington.

⁹Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh.

Address correspondence to Jason Sanders, BA, Bellefield Professional Building 4th Floor, 130 North Bellefield Avenue, Pittsburgh, PA 15213. Email: sanders.jason@medstudent.pitt.edu

Introduction. The correlation between dehydroepiandrosterone sulfate (DHEAS) decline and age led to the hypothesis that DHEAS might be a marker of primary aging, though conflicting data from observational studies of mortality do not support this. We evaluated concurrent DHEAS and functional decline in a very old cohort to test if DHEAS change tracks with functional change during aging.

Methods. DHEAS and functional performance (gait speed, grip strength, Modified Mini-Mental State Examination [3MSE] score, and digit symbol substitution test [DSST] score) were measured in 1996–1997 and 2005–2006 in 989 participants in the Cardiovascular Health Study All Stars study (mean age 85.2 years in 2005–2006, 63.5% women and 16.5% African American). We used multivariable linear regression to test the association of DHEAS decline with functional decline.

Results. After adjustment, each standard deviation decrease in DHEAS was associated with greater declines in gait speed (0.12 m/s, $p = .01$), grip strength (0.09 kg, $p = .03$), 3MSE score (0.13 points, $p < .001$), and DSST score (0.14 points, $p = .001$) in women only. Additional adjustment for baseline DHEAS attenuated the association with grip strength but did not alter other estimates appreciably, and baseline DHEAS was unassociated with functional decline.

Conclusions. In this cohort of very old individuals, DHEAS decline tracked with declines in gait speed, 3MSE score, and DSST score, but not grip strength, in women independent of baseline DHEAS level. DHEAS decline might be a marker for age-associated performance decline, but its relevance is specific to women.

Key Words: Aging—Biomarker—Dehydroepiandrosterone sulfate—Function.

Received November 25, 2009; Accepted April 14, 2010

Decision Editor: Luigi Ferrucci, MD, PhD

IN humans, the adrenal cortex secretes dehydroepiandrosterone sulfate (DHEAS), a steroid hormone, as a precursor to other sex steroid hormones. It has been hypothesized that DHEAS could be a biomarker of aging because in humans it decreases by 80%–90% between the third decade of life and older age (1–3). To test this hypothesis, previous researchers traditionally determined the association of a single DHEAS measurement with mortality in observational studies. Though low DHEAS has been associated with mortality in some human studies (4–7), the relationship remains unclear (4,6–10) and might even be U-shaped (11). Departing from previous study designs, Cappola and coworkers examined if the slope or variability of DHEAS was associated with mortality in

participants aged more than 65 years in the Cardiovascular Health Study (CHS). The results demonstrate that a smaller slope or less variability in DHEAS decline was predictive of lower mortality (12). Furthermore, prediction was independent of baseline DHEAS level, which itself was not associated with mortality. These results call into question how previous studies have modeled DHEAS, either as a single measurement, slope, or variance, and if the potential value of DHEAS as a biomarker of aging might be realized by modeling its change over the life span.

In addition to modeling DHEAS differently, it would be prudent to study the association of DHEAS to markers of aging other than mortality, such as functional decline. Here,

we examine if DHEAS change tracks with change in cognitive and physical performance, clinically relevant measures of health status in the elderly participants. To do so, we measured these factors in 1996–1997 and 2005–2006 in the Cardiovascular Health Study All Stars (CHS-All Stars) study, which was established to study functional aging in very old adults who participated in the CHS. Specifically, we hypothesized that DHEAS decline, but not baseline DHEAS, would be associated with functional decline.

METHODS

Study Population

CHS-All Stars study was designed to study the determinants of functional aging in long-term survivors of the CHS. CHS is a four-center, longitudinal, observational community-based study of the onset, progression, and course of cardiovascular disease in 5,888 older men and women (13,14). The CHS cohort was aged 65 years or older at enrollment in 1989–1990 and was supplemented with added minority participant recruitment in 1992–1993. Participants and eligible household members were identified from a random sample of Medicare enrollees at each field center. To be eligible, participants were aged 65 years and older, did not have cancer under active treatment, could not be wheelchair- or bed bound in the home, and did not plan to move out of the area within 3 years.

In 2005–2006, we re-recruited and evaluated 1,677 CHS participants for the CHS-All Stars study. Of these, in-person examination including DHEAS levels was obtained for 991 participants. To measure DHEAS change, we assessed DHEAS in these 991 individuals using blood samples from 1996–1997, resulting in 989 valid measurements used in this analysis. All procedures relating to CHS and CHS-All Stars study were approved by all participating institutions' institutional review boards.

Measurement of DHEAS

Plasma DHEAS was measured in samples drawn 9 years apart and analyzed as pairs in 2007 using a competitive immunoassay kit (Alpco Diagnostics, Windham, NH) with interassay coefficients of variation of 3.8%–7.2%.

Measurement of Physical and Cognitive Function

Physical function was measured using gait speed (meters per second) and grip strength (kilograms), as previously described (13). Cognitive function was evaluated with the Modified Mini-Mental State Examination (3MSE) (15) and digit symbol substitution test (DSST) scores (16). The 3MSE score is an expanded 100-point version of the original Folstein Mini-Mental State Examination. The DSST score is a measure of psychomotor speed and working memory (17).

Measurement of Covariates

From the baseline CHS examination (1989–1990) until 1998–1999, study participants completed up to 10 annual clinic visits and semiannual phone calls, after which phone follow-up was conducted semiannually until 2005–2006. Information collected at clinic visits included demographics, vital signs, anthropometric factors, medical history and behaviors, physical function, and psychosocial interviews (13). In 2005–2006, CHS-All Stars examinations were conducted and included measurement of physical and cognitive function, pulse, blood pressure, anthropometric factors, and medical history. Blood was collected and stored centrally (18). Body mass index (BMI) was calculated as the weight (kilograms)/height (meter square).

Hypertension was present if systolic blood pressure was 140 mmHg or more or diastolic pressure was 90 mmHg or more or if hypertension was reported as present with concomitant use of antihypertensive medication. Diabetes mellitus was classified using the American Diabetes Association criteria as not present, impaired fasting glucose, or diabetes (19). Cerebrovascular disease included stroke or transient ischemic attack. Coronary heart disease was present if one of the following was reported and confirmed: myocardial infarction, angina, history of angioplasty, or bypass surgery. Cardiovascular events were adjudicated by an expert panel using medical records, and medication information was updated at each examination (20). Chronic pulmonary disease (asthma, bronchitis, or emphysema), arthritis, cancer, and kidney disease were assessed by self-report of physician diagnosis. Depression was defined as a score more than 10 on a modified 10-item Center for Epidemiologic Studies Short Depression Scale test (21,22).

Statistical Analysis

We calculated the mean level of DHEAS and functional performance measures in 1996–1997 and 2005–2006 and the mean change over 9 years. We tested for a difference between men and women in baseline, follow-up, and change in mean DHEAS or functional performance using the Wilcoxon–Mann–Whitney test. Next, we categorized DHEAS change as less than 33%, 33%–66%, or more than 66% and calculated the mean functional performance decline in each category. We used linear regression to test the association of concurrent DHEAS decline as an independent variable with functional performance decline as the dependent variable. Models were adjusted for baseline (1996–1997) covariates. Model 1 included age (centered at the baseline mean 76.3 years), race, and smoking. Model 2 included covariates in Model 1 and additionally BMI, total cholesterol, total number of medications, hypertension, kidney disease, chronic pulmonary disease, cerebrovascular disease, coronary heart disease, diabetes, arthritis,

Table 1. Baseline Characteristics of the Study Population

Characteristics	Men (n = 361)	Women (n = 628)
Age, <i>M</i> (<i>SD</i>)	76.4 (3.5)	76.3 (3.6)
Black race, <i>n</i> (%)	56 (16)	106 (17)
Ever smoked, <i>n</i> (%)	233 (65)	226 (37)
BMI, <i>M</i> (<i>SD</i>) (kg/m ²)	27.0 (3.9)	27.3 (4.8)
Total cholesterol, <i>M</i> (<i>SD</i>) (mg/dL)	191 (36)	211 (36)
Number of medications, median (IQR)	2 (2)	3 (3)
Hypertension, <i>n</i> (%)	202 (56)	373 (59)
Kidney disease, <i>n</i> (%)	17 (5)	26 (4)
Chronic pulmonary disease, <i>n</i> (%)	55 (15)	138 (22)
Cerebrovascular disease, <i>n</i> (%)	15 (4)	31 (5)
Coronary heart disease, <i>n</i> (%)	79 (22)	100 (16)
Diabetes, <i>n</i> (%)	44 (12)	57 (9)
Arthritis, <i>n</i> (%)	239 (66)	493 (78)
Cancer, <i>n</i> (%)	91 (25)	103 (16)
Depression, <i>n</i> (%)	42 (12)	100 (16)

Note: BMI, body mass index; IQR, interquartile range.

cancer, and depression. Model 3 included covariates in Model 2 and additionally baseline DHEAS. Standardized regression coefficients were calculated. We tested for an interaction between gender and DHEAS in all models. We found significant interaction ($p < .05$) between gender and DHEAS in some models, so we stratified all models by gender for ease of interpretation. Stratification did not alter the magnitude or significance of the results despite the smaller sample size in each stratum. For comparability to previous studies, we were also interested to see if baseline DHEAS was associated with baseline functional performance or if baseline DHEAS was associated with functional decline. To study these associations, we repeated the above model schemes using only baseline DHEAS as the independent variable and either baseline function or functional decline as dependent variables. For all analyses, we used a significance level of $p < .05$ and SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Trends in DHEAS and Functional Performance During the Study Period

In 1996–1997, our sample was 63.5% women and 16.5% African American, and the *M* (*SD*) age was 76.3 (3.6) years. Baseline characteristics of the study population are presented in Table 1. DHEAS level in 1996–1997 and 2005–2006 and DHEAS decline were significantly greater in men versus women (Table 2). At baseline and follow-up, men had significantly faster gait speed, greater grip strength, and lower DSST score compared with women. 3MSE score was similar between genders at baseline and follow-up. Physical and cognitive performance decline were equivalent between genders except for grip strength, which declined more in men. Gait speed ($p < .0001$) and DSST score ($p = .0001$) appeared to decline significantly more with greater DHEAS decline in women, and grip strength ($p = .02$) appeared to decline

Table 2. Mean DHEAS and Functional Performance During the Study Period

Variable	Men		Women	
	<i>n</i>	<i>M</i> (<i>SD</i>)	<i>n</i>	<i>M</i> (<i>SD</i>)
DHEAS (µg/mL)				
1996–1997*		0.85 (0.52)		0.56 (0.41)
2005–2006*		0.66 (0.52)		0.48 (0.41)
Change*	361	–0.20 (0.32)	628	–0.08 (0.26)
Gait speed (m/s)				
1996–1997*		1.02 (0.23)		0.95 (0.22)
2005–2006*		0.81 (0.22)		0.73 (0.22)
Change	319	–0.23 (0.24)	545	–0.23 (0.24)
Grip strength (kg)				
1996–1997*		38.4 (7.6)		23.1 (5.6)
2005–2006*		29.8 (8.1)		17.8 (5.6)
Change*	342	–8.6 (5.6)	590	–5.3 (4.5)
3MSE score				
1996–1997		95.3 (4.7)		95.2 (5.3)
2005–2006		88.4 (11.4)		88.8 (10.8)
Change	361	–6.8 (10.0)	628	–6.3 (9.0)
DSST score				
1996–1997*		41.5 (11.9)		45.0 (11.9)
2005–2006*		31.1 (13.2)		33.6 (13.8)
Change	355	–10.4 (9.2)	606	–11.2 (10.5)

Notes: DHEAS, dehydroepiandrosterone sulfate; DSST, digit symbol substitution test; 3MSE, Modified Mini-Mental State Examination.

* $p < .05$ for gender comparison.

significantly more with greater DHEAS decline in men (Table 3).

Association Between DHEAS Decline and Functional Performance Decline

Greater DHEAS decline was significantly associated with greater declines in gait speed, grip strength, 3MSE, and DSST scores in women (Table 4). Adjustment for baseline DHEAS attenuated the association with grip strength to nonsignificance but did not substantially alter other associations. Additionally, there was no interaction between baseline DHEAS and DHEAS decline. In the final models, baseline DHEAS was not associated with performance decline, and the significant association between DHEAS decline and performance decline was not attenuated by baseline DHEAS.

Association Between Baseline DHEAS and Functional Performance or Functional Performance Decline

Baseline DHEAS was not associated with baseline functional performance or functional performance decline before or after adjustment for sociodemographic and health characteristics in men or women ($p > .05$ for all functional outcomes).

DISCUSSION

We found that on average, in this population of very old individuals, DHEAS and functional performance decreased over 9 years. Greater DHEAS decline was significantly

Table 3. Mean Change in Functional Performance by DHEAS Decline Groups

% DHEAS Decline	Mean Change in Functional Performance*			
	Gait Speed (m/s)	Grip Strength (kg)	3MSE Score	DSST Score
Men				
<33	-0.22 (-0.25 to -0.18)	-8.6 (-9.3 to -7.8)	-7.0 (-8.3 to -5.6)	-10.3 (-11.6 to -9.0)
33-66	-0.24 (-0.28 to -0.19)	-8.3 (-9.3 to -7.3)	-6.7 (-8.5 to -4.9)	-10.5 (-12.2 to -8.8)
>66	-0.24 (-0.37 to -0.10)	-13.1 (-16.3 to -9.9)	-6.2 (-11.7 to -0.6)	-10.7 (-15.8 to -5.6)
Women				
<33	-0.20 (-0.23 to -0.18)	-5.1 (-5.5 to -4.7)	-6.1 (-6.9 to -5.2)	-10.1 (-11.1 to -9.1)
33-66	-0.29 (-0.33 to -0.25)	-5.8 (-6.5 to -5.0)	-6.9 (-8.4 to -5.4)	-13.3 (-15.1 to -11.5)
>66	-0.35 (-0.44 to -0.26)	-5.6 (-7.1 to -4.0)	-7.3 (-10.3 to -4.4)	-15.9 (-19.3 to -12.5)

Notes: DHEAS, dehydroepiandrosterone sulfate; DSST, digit symbol substitution test; 3MSE, Modified Mini-Mental State Examination.
 *Mean (95% confidence interval) is presented.

associated with greater decline in gait speed and 3MSE and DSST scores in women. These associations were independent of baseline DHEAS. These data suggest that DHEAS decline tracks with decline in physical and cognitive performance in women. Consequently, the rate of DHEAS decline might be a marker of functional aging in very old women.

These findings support the hypothesis that declines in both DHEAS and function might reflect shared processes, such as oxidation or inflammation, which appear to underlie aging. In vivo and in vitro data have established that DHEAS in the brain exerts neuroprotective effects through its role as an antioxidant, neuronal growth stimulant, and proponent of neuronal survival following stress (23,24). There is also strong evidence that DHEAS and its highly active steroid derivatives serve as an anti-inflammatory pool and directly and/or indirectly modulate proinflammatory molecules,

such as interleukin-6, tumor necrosis factor-alpha, and nuclear factor-kappa B, and immune states, such as shifting the immune profile from a T_H2 to T_H1 response (23,25). Subsequently, as DHEAS decreases with age, inflammatory mechanisms might be derepressed and oxidants might not be scavenged effectively. Increased inflammation has also been associated with functional decline (26). Therefore, DHEAS decline and functional decline might be related through these processes, with DHEAS decline as a possible cause of increasing inflammation over the life span and functional decline as a consequence of increased inflammation. Alternatively, oxidation could simultaneously spur declines in DHEAS and function. Because we measured DHEAS and function concurrently, we cannot draw mechanistic conclusions. A recent randomized placebo-controlled trial of DHEA supplementation in older men and women demonstrated no effect on body composition, peak oxygen consumption, muscle strength, insulin sensitivity, or quality of life, though men increased slightly in free fat mass and femoral neck bone mineral density and women increased ultradistal radius bone mineral density (27). Further research is needed to define shared risk factors for DHEAS and functional decline. It is possible that DHEAS might be more useful for monitoring aging than as a point of intervention.

We found that DHEAS decline might be a better indicator of cognitive aging than physical aging. We found that DHEAS decline tracked with declines in 3MSE and DSST scores, clearly illustrating an association with cognitive decline. The association with physical decline was less consistent, being significant with gait speed but not grip strength. Because walking is a more complex task than gripping and requires greater cognitive input, it could be that DHEAS decline was associated with gait speed decline circumferentially through the cognitive contribution to walking (28,29). Future DHEAS studies should be conducted with an understanding that the statistical significance of results might be influenced by whether outcomes are chiefly governed by cognitive or physical input.

Our results not only agree with some of the few previous studies of the relationship between DHEAS and functional

Table 4. Association of DHEAS Decline With Functional Performance Change*

Performance Change	Model 1 [†]		Model 2 [‡]		Model 3 [§]	
	β (SE)	p	β (SE)	p	β (SE)	p
Men						
Gait speed (m/s)	.06 (0.06)	.30	.07 (0.07)	.25	.06 (0.07)	.36
Grip strength (kg)	.09 (0.06)	.11	.10 (0.07)	.08	.07 (0.07)	.28
3MSE score	-.01 (0.05)	.88	-.03 (0.06)	.54	-.04 (0.06)	.57
DSST score	-.08 (0.05)	.14	-.09 (0.06)	.12	-.07 (0.06)	.26
Women						
Gait speed (m/s)	.13 (0.04)	.003	.12 (0.05)	.009	.12 (0.05)	.01
Grip strength (kg)	.10 (0.04)	.02	.09 (0.05)	.03	.06 (0.05)	.18
3MSE score	.13 (0.04)	.0008	.13 (0.05)	.0009	.12 (0.05)	.007
DSST score	.15 (0.04)	.0003	.14 (0.05)	.001	.13 (0.05)	.007

Notes: BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; DSST, digit symbol substitution test; 3MSE, Modified Mini-Mental State Examination.

*Linear regression coefficients illustrate the difference in average performance decline for each standard deviation decline in DHEAS (0.32 μg/mL for men and 0.26 μg/mL for women).

[†]Adjusted for age, race, and smoking. Age was centered at the baseline mean (76.3 years).

[‡]Adjusted for covariates in Model 1 and additionally for BMI, total cholesterol, total number of medications, hypertension, kidney disease, chronic pulmonary disease, cerebrovascular disease, coronary heart disease, diabetes, arthritis, cancer, and depression.

[§]Adjusted for covariates in Model 2 and additionally for baseline DHEAS.

outcomes but also suggest that a lack of longitudinal data may explain the lack of associations in previous studies. In 622 participants aged more than 65 years, Berr and coworkers (6) found no association between DHEAS and cognitive function. In a study of approximately 450 men and women, Barrett-Conner and Edelman (9) documented that baseline DHEAS was not associated with four of five tests of later cognitive ability. Our data indicate that using baseline DHEAS as a predictor or a cross-sectional design yield null associations between DHEAS and function. Goldman and Gleib (30) illustrated that baseline DHEAS was associated with subsequent physical and cognitive decline in men ($n = 472$, mean age 66 years) but not in women ($n = 364$, mean age 65 years), which we did not observe. This discrepancy could be because the study population of Goldman and Gleib was younger with a wider range of DHEAS levels or because they relied on 3 years of follow-up time rather than our 9 years. It is also possible that differences in the measures of physical and cognitive decline explain these differences (30). Notably, Mazat and coworkers (7) reported that DHEAS change over 6 years, but not DHEAS at a single point in time, was correlated with Mini-Mental State Examination score in a cohort of 290 participants (mean age ~74 years), which is similar to our findings. Finally, in a cross-sectional study, Haren and coworkers (31) found that DHEAS in 124 50- to 65-year-old African American men was directly associated with performance on the Mini-Mental State Examination. It is difficult to compare Haren's results to our own due to the vastly different age, race, and health backgrounds of study participants. Taken in context with our results, it appears that associations between DHEAS and function are most appropriately modeled using longitudinal rather than cross-sectional data.

The main strengths of this study were the large sample size, adjustment for numerous potential confounders, and use of longitudinal modeling. An important limitation of this study is that the cohorts studied represent survivors of a long-term cohort study and were healthier than nonsurvivors although not much healthier than survivors who did not participate in the examination (32). It is likely that declines in DHEAS and function were even greater in nonsurvivors, which would tend to bias associations toward the null. It should also be noted that the changes observed were small relative to the variability in the assay. Assays were paired to minimize variability. Finally, we present associations between absolute changes but would point out that adjustment for baseline DHEAS and correlates of function did not attenuate the associations.

In conclusion, we demonstrate that DHEAS decline and performance decline track together in very old adults. We hypothesize that decline in these factors might be associated directly or through changes in common risk factors, possibly inflammation and oxidation. Thus, DHEAS might be a useful marker of aging by capturing phenomena, which

appear to affect overall function. The usefulness of DHEAS as a marker, though, might be confined to women and better in predicting cognitive rather than physical performance decline. Future research that models rates of change across a greater age span would aid description of the association between DHEAS and functional performance in older adults.

FUNDING

The research reported in this article was supported by the National Institute on Aging AG-023629. CHS was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01-HC-55222, N01-HC-75150, and N01-HC-45133, grant number U01-HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through R01-AG-15928, R01-AG-20098, and AG-027058 from the National Institute on Aging, R01-HL-075366 from the National Heart, Lung and Blood Institute, and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center P30-AG-024827.

ACKNOWLEDGMENTS

A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/pi.htm>.

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