

**New evidence for protective effects of DHEAS on health  
among men but not women**

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Abbreviations: DHEA=Dehydroepiandrosterone;  
DHEAS=Dehydroepiandrosterone-sulfate; SEBAS=Social Environment and Biomarkers of Aging Study; CES-D= Center for Epidemiologic Studies Depression scale

## ABSTRACT

The adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS) have been the focus of considerable publicity in recent years because of their demonstrated associations with a broad range of health outcomes. Yet, despite a large literature examining the health consequences of DHEA(S), few have been based on prospective surveys of population-representative samples. Thus, our knowledge about the causal effects of DHEA(S) on health in humans is limited and often inconclusive. In this analysis, we use a national longitudinal survey in Taiwan to explore the associations between DHEAS and changes over a 3-year period in functional limitations, cognitive impairment, depressive symptoms, and global self-rated health for men and women.

Our estimates suggest that, for the older Taiwanese population, DHEAS is related to subsequent declines in mobility and increased depressive symptoms among men, but there are no significant associations between DHEAS and women's mental and physical health. These findings differ from those in a previous *cross-sectional* analysis based on the Taiwan study and underscore the importance of using prospective rather than cross-sectional data to examine the effects of DHEAS on health. The evidence to date from this study and other investigations based on longitudinal data suggests that DHEAS is protective of some health outcomes for men, but not women, in both Western and non-Western populations and raises questions about what factors give rise to these sex differences.

## INTRODUCTION

The adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS) have been the focus of considerable publicity in recent years because of their demonstrated associations with a broad range of health outcomes and extrapolated claims that, taken as nutritional supplements, they may enhance longevity. These inactive prohormones are secreted in large amounts by the adrenal cortex only in humans and in other primates and are converted to androgens and estrogens in peripheral tissues (1). The steady decrease in serum levels of these steroids from early adulthood onwards suggests that they may be markers of aging and that high levels may protect against the pathological consequences of becoming old. Animal experiments reveal broad-ranging health effects of DHEA and DHEAS, and experimental and observational studies on humans demonstrate statistically significant associations with survival and various measures of health status, including diabetes, cardiovascular disease, obesity, cognitive impairment, physical limitations and depressive symptoms (see, for example, 2-8).

In light of the fact that DHEA and DHEAS are precursors to sex hormones, it is not surprising that there appear to be important differences between men and women. Virtually all studies find that the concentration of these steroids is much higher in men than in women and many find that the associations between DHEA(S) and health or survival vary by sex. However, these latter findings are often contradictory, with some studies suggesting associations only among males, others finding no significant differences by sex, and two studies reporting stronger associations among women than men for selected outcomes (5, 9).

Despite extensive research on these steroids, little is known about their specific functions or the mechanisms by which they affect health (10). Research suggests that DHEA may counterbalance the immunosuppressive effects of glucocorticoids, although the receptor for DHEA has not been fully characterized (11). DHEA has been shown to have biological actions on hemostasis, cell proliferation, lipid metabolism, stress response, and immune function (6, 12). Knowledge about causal effects of DHEA(S) for health in humans is limited and often inconclusive for several reasons: many of the experimental studies have been performed on non-primates, which have far lower concentrations of these steroids than humans (13, 14); experimental studies in humans have typically involved short-term administration of pharmacological doses, small samples, and subjects with various disorders, such as adrenal insufficiency (13-18); and observational studies of humans have been primarily cross-sectional, preventing researchers from separating what are believed to be the effects of certain illnesses on DHEA(S) levels from the sought after effects of DHEA(S) on health status (19, 20).

Surprisingly few studies have been based on prospective surveys of population-representative samples, despite the advantage of this research design for investigating the effects of endogenous levels of DHEA(S) on health in the general population (5, 6, 21, 22). Moreover, virtually all of the longitudinal population-based surveys that have been carried out are based on community samples of (predominantly) whites in the United States or Western Europe, thereby limiting generalizations to broader populations because of racial and ethnic differences in concentrations of DHEAS and adrenal metabolism (19, 22). Many have additional limitations, including restriction to one sex

(6, 23, 24) and small, selective, or non-representative samples (e.g., high non-response rates, selection of healthy subjects, and non-random selection from larger samples; 5, 7, 23, 25-27). In addition, many of these surveys focus on survival, providing less information on the consequences of varying levels of DHEA(S) for other important outcomes related to physical and mental well-being.

In the present analysis, we use the 2000 Social Environment and Biomarkers of Aging Study (SEBAS) to explore the associations between DHEAS and declines over a 3-year period in functional limitations, cognitive impairment, depressive symptoms, and global self-rated health. This longitudinal survey is based on a random national sample of persons aged 54 and older in Taiwan, providing – to the best of our knowledge – the first set of population-based estimates of these associations for a non-Western society and one of the few prospective data sets to permit comparisons between men and women across a broad range of health outcomes. Because these data contain extensive information regarding health and socio-demographic characteristics at baseline, the resulting estimates are less likely than those from other studies to be plagued by biases due to confounding and reverse causality.

## **METHODS**

**Data.** The data come from the 2000 Social Environment and Biomarkers of Aging Study (SEBAS), which comprises a national sub-sample of respondents interviewed as part of Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan (28). The longitudinal survey began in 1989 with a national sample of 4049 persons aged 60 and older (response rate, 92%), and was expanded in 1996 to include 2462 near elderly persons aged 50 to 66 in 1996 (response rate, 81%). Both cohorts were interviewed in 1999 (response rate, 90% of survivors). Among those interviewed in 1999, a random sub-sample was selected for the 2000 SEBAS, with an oversampling of persons 71 years and older (in 2000) and residents of urban areas. In 2003, survivors of the SEBAS sample were interviewed (response rate, 97% for participants in the medical exam). Details regarding survey attrition are presented in Gleib and Goldman (29).

SEBAS consisted of an in-home interview and a hospital examination: 1497 persons aged 54 and older provided interviews in SEBAS (92% of survivors) and 1023 participated in the physical examination (68% of those interviewed). Disproportionately high non-participation rates were found among the healthiest respondents as well as the least healthy, with persons who received the medical exam reporting the same average health status (measured on a five-point scale) as those who did not. Results presented elsewhere (30) suggest that, in the presence of controls for age, estimates derived from the medical exam portion of SEBAS are unlikely to be seriously biased.

SEBAS respondents who participated in the medical exams collected a 12-hour overnight urine sample (7pm to 7am, in order to obtain integrated values of cortisol and catecholamines), fasted overnight and visited a nearby hospital the following morning. During the hospital visit, medical personnel drew a blood sample and took blood pressure and anthropometric measurements. Written informed consent was obtained for participation in the interview and physical examination. Almost all exam participants provided suitable specimens.

Blood and urine specimens were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to the routine standardization and calibration tests performed by the laboratory, during the early stages of fieldwork nine individuals (outside of the target sample) contributed triplicate sets of specimens. In each case, two sets were submitted to UCL and a third was sent to Quest Diagnostics in the US. The results for DHEAS and urinary cortisol indicate high inter- and intra-lab reliability (intra-lab correlations  $\geq 0.88$ ; inter-lab correlations  $\geq 0.95$ ).

**Measures.** We examine four outcomes capturing different dimensions of health status in 2003: depressive symptoms, cognitive impairment, mobility limitations and global self-rated health. Depressive symptoms are measured by a 10-item short form of the full CES-D (Center for Epidemiologic Studies Depression) scale, coded according to standard practice based on both the number and severity of symptoms (potential range from 0 to 30). Previous studies have demonstrated that a shortened form of the CES-D yields similar internal consistency, factor structure, and accuracy in detecting depressive symptoms as the full 20-item CES-D among elderly Chinese (31). Cognitive impairment is based on items from the modified Short Portable Mental Status Questionnaire (32), the modified Rey Auditory Verbal Learning Test (33), and a modification of the Digits Backward test (34). The measure is a count of the number of cognitive tasks completed incorrectly, including basic orientation questions, a series of four subtractions, and immediate memory recall (potential range from 0 to 24). The measure of mobility limitations counts the number of physical tasks, out of the following nine, that the respondent reports difficult performing without aid: standing continuously for 15 minutes and for two hours, squatting, raising both hands over his or her head, grasping or turning objects with his or her fingers, lifting or carrying an object weighing 11-12 kg., running a short distance (20-30 meters), walking 200-300 meters, and climbing two or three flights of stairs. Global SRH is based on the following question: “Regarding your current state of health, do you feel it is excellent, good, average, not so good, or poor?” This five-point ordinal measure is scored so that five indicates “poor” health.

The key independent variable is serum DHEAS in 2000, assayed using radioimmunoassay (35), with an inter-assay coefficient of variation of 12.9 and sensitivity of 1.1  $\mu\text{g}/\text{dL}$ . We chose to measure DHEAS rather than DHEA because DHEAS is cleared less rapidly from the bloodstream and has less diurnal variation (36). We include urinary cortisol as a control variable because DHEAS is believed to act as an antagonist to the effects of cortisol, extreme levels of cortisol are related to numerous chronic conditions, and concentrations of these two steroids may be correlated (11, 27, 37-39). Cortisol is based on the 12-hour urine sample and measured in micrograms per gram creatinine to adjust for body size. Assays of urinary cortisol were made by high pressure liquid chromatography (40, 41), with a lower detection limit of 4  $\mu\text{g}/\text{L}$ . Because outliers may have undue influence on the estimates, we trimmed several values ( $n=3$  for DHEAS;  $n=1$  for cortisol) to five standard deviations above the mean.

Additional control variables include age, sex, smoking, residence in an urban area, and baseline health status. Age is modeled as a continuous variable; a quadratic term is also included when it is statistically significant. Smoking status in 2000, based on the previous six months, distinguishes those who did not smoke, those who smoked fewer than 20 cigarettes daily, and those who smoked 20 or more cigarettes daily. Although the

mechanisms are not understood, numerous studies have found smoking to be positively related to DHEAS (2, 8, 36, 42-44). Measures of the four outcome variables assessed in 2000 are included to control for baseline health status.

Because results from earlier research suggest that the effects of DHEAS levels on health may be significant for men but not for women, we include interaction terms between DHEAS levels and sex in each of the models. In exploratory analyses, we also considered the inclusion of a variable for alcohol consumption as well as interaction terms between sex and cortisol level, but because these terms were not significantly different from zero, they are not included in the final models.

**Analytical Strategy.** The statistical analysis is based on the 926 SEBAS participants who were interviewed in 2003. Exclusion of respondents who were missing information on any of the four health outcomes or the explanatory variables resulted in an analysis sample of 841 respondents.

Multivariate models are based on unweighted data, but include age and urban residence to adjust for the sampling design. Because of the multistage sampling design, we use a robust estimator of variance and adjust for clustering by primary sampling units to produce correct standard errors (45). We estimate a linear regression model for the depressive symptom score, Poisson models for the two count measures (cognitive impairment and mobility limitations) and an ordered logit model for SRH. Because about one-third of respondents had zero mobility limitations, we use a zero-inflated Poisson model (ZIP) (46), which provides a much better fit than the standard Poisson model, for this outcome.

## RESULTS

Table 1 provides descriptive statistics of the four outcome variables measured in 2003, DHEAS, the baseline health variables, cortisol, and other control variables, all measured in 2000; these statistics are weighted for the over-sampling by age and urban residence. Values for the health variables indicate that, on average, respondents reported poorer health in 2003 than in 2000 (e.g., 2.2 vs. 1.8 mobility limitations). Levels of DHEAS are substantially higher among men than women, declining progressively for men throughout this age range and for women below age 75. These values are comparable to those for some, but not all, samples in Western populations (9). The percentage of the sample that is female (44%) is atypically low because of the substantial migration of Nationalists, primarily soldiers, from Mainland China in the late 1940s.

Results from the multivariate models are presented in Table 2. Because higher values denote poorer health for all four outcomes, we expect negative coefficients for DHEAS. To facilitate comparisons by sex, we show separate DHEAS estimates for men and women, derived from the main effect of DHEAS and the interaction between DHEAS and sex. For men, the coefficients reveal a significant ( $p < 0.05$ ) negative association between levels of DHEAS and both mobility limitations and depressive symptoms, a borderline significant association for self-rated health (SRH) ( $p < 0.10$ ), and no association for cognitive impairment. In contrast, none of the associations between DHEAS and health measures is significant for women. With the exception of a borderline

significant association for mobility limitations ( $p < 0.10$ ), cortisol is not significantly associated with the health outcomes.

In order to assess the magnitude of the associations, in Table 3 we present predicted values for the two health outcomes among males that are significantly associated with levels of DHEAS. These predictions are obtained by assigning specified values of DHEAS to all observations (based on the percentile distribution among males), assigning sex as male, retaining other explanatory variables at their observed values, and using the coefficients from the models in Table 2 to obtain the predictions. The predictions underscore the substantial variation in mobility limitations and depressive symptoms for varying concentrations of DHEAS among men: values of DHEAS at the 90<sup>th</sup> percentile are associated with almost one (0.8) fewer mobility limitation and depressive symptom than values at the 10<sup>th</sup> percentile.

## DISCUSSION

Our estimates suggest that, for the older Taiwanese population, DHEAS is related to subsequent declines in some dimensions of men's (but not women's) psychological and physical health. Exploratory analyses reveal that these results are generally robust to the use of log-transformed levels of DHEAS and to inclusion or exclusion of outliers. Researchers have speculated that estimated effects of DHEAS on health may be biased because of failure to include information on cardiovascular risk factors that may be correlated with DHEAS, although it is unclear whether these factors are potential confounders or whether they are mediators linking DHEAS and health (19, 21, 22, 47). We added a set of cardiovascular markers – diastolic and systolic blood pressure, total and HDL cholesterol, glycosylated hemoglobin, BMI, and waist-hip ratio – to our statistical models (data not shown), but the estimated coefficients of DHEAS remained virtually unchanged for both sexes.

These findings differ from those in a previous *cross-sectional* analysis based on the Taiwan study that found larger associations between DHEAS and mobility limitations and cognitive function for women than for men (9). Although the present analysis uses the same measures of DHEAS as the earlier study, health outcomes in the earlier study were assessed at roughly the same time as the biological measures. We speculate that inconsistencies between the two sets of estimates may result from sex differences in the extent to which a correlation between DHEAS and health results from reverse causality (that is, from the impact of disease on levels of DHEAS). Although there is some evidence that DHEA(S) levels decrease during illness (19, 20, 48), there are few insights into how or whether this process differs by sex. Numerous correlation analyses relating health status to measures of DHEAS for men and women shed little light on the issue, both because the time sequence of cause and effect is unclear and because the patterns by sex vary enormously across studies. For example, Berr et al. (5) found that measures of functional and psychological status had stronger associations with levels of DHEAS in women, whereas Tilvis et al. (49) identified stronger associations between various diseases and levels of DHEAS in men. We used data from the earlier rounds of the Taiwan survey to examine the effects of changes in health during 1999-2000 and 1996-2000 on levels of DHEAS in 2000 and found evidence that an increase in mobility limitations over these periods was associated with a decrease in DHEAS for women but

not men – a finding that is consistent with the stronger (but spurious) DHEAS associations identified for women in the cross-sectional analysis (9).

These findings underscore the importance of using prospective rather than cross-sectional data to examine the effects of DHEAS on health. In Table 4, we summarize the few prospective studies that examine all-cause mortality or one of the four broad health outcomes explored in this paper. The studies, most of which examine survival or cognitive impairment, offer mixed evidence on the protective effects of DHEAS on men's health. Findings for women are more clear-cut: there is only one study (24) suggesting that DHEAS has a protective effect for women. These findings are consistent with conclusions in several review articles on sex differences in the effects of DHEA(S) on fatal and nonfatal cardiovascular outcomes (21, 43, 47) as well as with our results for Taiwan.

Thus, the evidence to date suggests that DHEAS is protective of some health outcomes for men, but not women, in both Western and non-Western populations. In light of the uncertainty surrounding the biological functions and operating mechanisms of DHEA(S), it is not surprising that we know so little about sex differences in its effects. Numerous researchers have speculated that the apparent sex differences may result from differences between men and women in health-related behaviors (e.g., smoking or drinking) or cardiovascular risk factors (7, 42). However, based on exploratory analyses (not shown) using SEBAS data on smoking, drinking and the cardiovascular risk factors described above, we find no evidence to support these hypotheses. Thus, we are left with vague explanations, similar to those proposed by others, pertaining to potential sex differences in DHEAS concentration and excretion rates, as well as differences between men and women in hormonal metabolism and sex steroid environments (7, 8, 22, 50).

Limitations of the present study include the shortness of the follow-up period and reliance on serum DHEAS measured at one point in time. The latter issue is of particular concern because concentrations of DHEAS differ from those of DHEA and because measured concentrations of DHEA(S) are likely to depend on the type of assay and vary over time (22, 24). Future waves of SEBAS will include a second measurement of DHEAS in 2006-2007, additional biomarkers, and information pertaining to health and survival in subsequent years. These data will permit more sophisticated analyses that distinguish between the effects of DHEAS on changes in health and those of illness on changes in DHEAS over a longer time interval. Despite the potential advantages of this type of study, more in-depth biomedical analysis will be required to enhance our understanding of the marked reductions in adrenal secretion of DHEA(S) with advancing age, the mechanisms that result in such a broad range of physiological effects, and how and why these effects differ between men and women.

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**Table 1. Descriptive Statistics for All Measures, Weighted Analyses**

<b>Variable</b>	<b>Observed Range</b>	<b>Mean/ Percent</b>	<b>SD</b>
DHEAS in 2000 ( $\mu\text{g/dl}$ ) <sup>a</sup>	0-388	82.5	59.6
Males			
Age 54-59	11-388	123.5	78.2
Age 60-64	16-231	104.9	52.8
Age 65-69	2-386	93.4	66.8
Age 70-74	11-361	85.8	51.8
Age 75+	4-302	80.7	50.6
Females			
Age 54-59	0-215	73.2	46.0
Age 60-64	0-271	58.6	42.6
Age 65-69	0-223	54.4	44.8
Age 70-74	0-162	47.3	39.4
Age 75+	1-160	55.4	37.1
<b><u>Covariates in 2000</u></b>			
Age (years)	54-91	65.6	7.6
Female	0,1	43.6%	--
Urban residence	0,1	44.1%	--
Smoking status past six months:			
Did not smoke	0,1	76.6%	--
Smoked < 20 cigarettes/day	0,1	11.1%	--
Smoked $\geq$ 20 cigarettes/day	0,1	12.3%	--
Cortisol ( $\mu\text{g/g creatinine}$ ) <sup>b</sup>	2-281	26.2	28.1
Number of mobility limitations	0-9	1.8	2.2
CES-Depression scale	0-28	5.2	5.2
Number of cognitive impairments	0-21	7.0	3.2
Self-assessed health status	1-5		
Excellent (1)		13.0%	--
Good (2)		12.9%	--
Average (3)		48.3%	--
Not so good (4)		23.0%	--
Poor (5)		2.8%	--
<b><u>Health Outcomes in 2003</u></b>			
Number of mobility limitations	0-9	2.2	2.5
CES-Depression scale	0-29	5.2	5.5
Number of cognitive impairments	0-24	8.5	3.8
Self-assessed health status	1-5		
Excellent (1)		10.8%	--
Good (2)		22.3%	--
Average (3)		35.2%	--
Not so good (4)		28.0%	--
Poor (5)		3.7%	--
Number of cases	841		

<sup>a</sup> A few cases (n=7) were assigned a value of 0 on DHEAS because the level was below the sensitivity of the assay (1.1 ug/dl) and could not be detected. Three outliers on DHEAS (416.2, 440.9, and 496.6 µg/dl) were trimmed to five standard deviations above the mean.

<sup>b</sup> One outlier on cortisol (1291 µg/g creatinine) was trimmed to five standard deviations above the mean.

**Table 2. Relationship between Health Outcomes in 2003 and DHEAS in 2000 Based on Multivariate Models<sup>a</sup>, Unweighted Analyses**

	Mobility Limitations	CES-D	Cognitive Impairment	Poor Self-Assessed Health
DHEAS (µg/dl): Females <sup>b</sup>	0.001	0.005	0.000	0.001
	(0.001)	(0.009)	(0.000)	(0.001)
DHEAS (µg/dl): Male <sup>b</sup>	-0.003** <sup>c</sup>	-0.008*	0.000	-0.002+
	(0.001)	(0.003)	(0.000)	(0.001)
Cortisol (µg/g creatinine)	0.001+	0.001	-0.000	0.001
	(0.001)	(0.007)	(0.001)	(0.001)

Note: Robust standard errors are shown in parentheses.

+ p<0.10; \* p<0.05; \*\* p<0.01;

<sup>a</sup>Models adjust for all the covariates shown in Table 1.

<sup>b</sup>For variables with sex interactions, we show the total effect for males (equivalent to the main effect) and females (equivalent to the sum of the main and the interaction effect).

<sup>c</sup>Sex difference in the parameter estimate is significant (p<0.05).

**Table 3. Predicted Values for Health Outcomes at the 10<sup>th</sup>, 25<sup>th</sup>, 75<sup>th</sup>, and 90<sup>th</sup> Percentile Values of DHEAS for Males**

	Mobility	
	Limitations	CES-D
10 <sup>th</sup> percentile (DHEAS=33.1 )	2.26	5.52
25 <sup>th</sup> percentile (DHEAS=55.7)	2.11	5.34
75 <sup>th</sup> percentile (DHEAS=129.8)	1.68	4.74
90 <sup>th</sup> percentile (DHEAS=178.2 )	1.45	4.35

Note: Predicted values are calculated by setting DHEAS to the specified values, assigning sex as male, and leaving all other covariates at their observed values in the sample.

**Table 4. Summary of Results from Longitudinal Studies with Population-Based Samples Regarding the Relationship between DHEAS and Health**

Health outcome	Males		Females	
	SEBAS (Taiwan) <sup>a</sup>	Other studies	SEBAS (Taiwan) <sup>a</sup>	Other studies
All-cause mortality	N.S.	NEG (4 of 7) <sup>b,c,d,f</sup> POS (1 of 7) <sup>e</sup> N.S. (2 of 7) <sup>g,h</sup>	N.S.	POS (1 of 6) <sup>e</sup> N.S. (5 of 6) <sup>b,c,f,g,h</sup>
Functional limitations	NEG	n/a	N.S.	n/a
Depressive Symptoms	NEG	N.S. (1 of 1) <sup>c</sup>	N.S.	NEG (1 of 2) <sup>i</sup> N.S. (1 of 2) <sup>c</sup>
Cognitive Impairment	N.S.	NEG (1 of 3) <sup>c</sup> N.S. (2 of 3) <sup>b,j</sup>	N.S.	N.S. (3 of 3) <sup>b,c,j</sup>
Poor Self-Assessed Health Status	N.S.	N.S. (1 of 1) <sup>c</sup>	N.S.	N.S. (1 of 1) <sup>c</sup>

NEG=Negative relationship ( $p<0.05$ ); POS=Positive relationship ( $p<0.05$ ); N.S.=No significant relationship; n/a=No studies available

<sup>a</sup>Results for mortality are based on Gleib and Goldman (2006); results for other health outcomes come from Table 2.

<sup>b</sup>Berr et al. (1996); the original cohort ( $n=2792$ ) comprises a population-based sample, but analyses are based on a sub-sample ( $n=622$ ) of volunteers who agreed to have blood sampling; <sup>c</sup>Mazat et al. (2001); see comment for Berr et al. (1996); <sup>d</sup>Barrett-Connor et al. (1986); <sup>e</sup>Barrett-Connor et al. (1995); <sup>f</sup>Trivedi & Khaw (2001); <sup>g</sup>Tilvis et al. (1999); <sup>h</sup>Birkenhäger-Gillesse et al. (1994); <sup>i</sup>Yaffe et al. (1998); <sup>j</sup>Barrett-Connor & Edelstein (1994), Note: Study examined five measures of cognitive function; DHEAS significant for only one of these outcomes and only for females.