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Dehydroepiandrosterone sulfate (DHEAS) and health: does the relationship differ by sex?

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Abstract

This study uses data from a large, nationally representative sample of older Taiwanese (aged 54 and older in 2000) to investigate sex differences in the relationship between DHEAS and various health outcomes. Data collection included an individual interview, a physical examination, and samples of blood and (12-h) urine. Regression models of health outcomes on DHEAS are estimated in two steps: first, including only controls for age and sex as well as an interaction between DHEAS and sex; and second, adding covariates likely to be related to both DHEAS and health outcomes (e.g. smoking). Results reveal that higher levels of DHEAS are associated with fewer mobility limitations (especially for women), better cognitive function (among women but not men), and better self-rated health (significant only for men but of similar magnitude for women). These findings are in contrast to previous studies conducted in the US and Europe that generally find stronger associations for men than women. Also unlike previous studies, which often demonstrate a negative relationship between DHEAS and depressive symptoms at least for women, we find little evidence of such a relationship for either sex.

Keywords: Dehydroepiandrosterone sulfate; Health outcomes; Sex differences; Morbidity; Physical mobility; Cognitive function; Depression; Self-rated health

1. Introduction

The adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate form DHEAS[1] have attracted considerable interest in recent years. Because there are marked declines in DHEAS with age (Orentreich et al., 1984; Šulcová et al., 1997), researchers suspect it may be a marker of the aging process and potential longevity (Lopez, 1984; Kalimi and Regelson, 1999; Roth et al., 2002; Rotter et al., 1985; Rudman et al., 1990; Thomas et al., 1994; Yen, 2001). Viewed by some as a potential fountain of youth, DHEA supplementation has been reputed to prevent or ameliorate a myriad of illnesses and to enhance wellbeing (Baulieu et al., 2000; Morales et al., 1994; Shealy, 1995; South, 2002; Wolkowitz et al., 1997; Yen et al., 1995).

We investigate sex differences in the association between serum DHEAS and various health outcomes among the elderly in Taiwan. The data come from a large, nationally representative sample and are unusually rich, including a wide range of physical, psychological, and cognitive health outcomes, as well as biological markers. The breadth of data collected allow us to examine a broad range of health outcomes using the same sample, thereby eliminating sample selection as a potential source of observed differences across outcomes. All previous studies on this topic were conducted in the US or Europe; the Taiwanese context may provide important clues about these relationships in a non-Western population.

Although the literature documents an association between DHEAS and mortality as well as various indicators of health and morbidity, the results often differ by sex and in some cases, are contradictory (see Table 1). Previous studies demonstrate a negative relationship between DHEAS and

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[1] DHEAS is synthesized from DHEA but can also be metabolized back into DHEA (Regelson et al., 1994; Kishimoto and Hoshi, 1972). Typically, DHEAS is measured instead of DHEA because it is less rapidly cleared from the bloodstream and has less diurnal variation (Kroboth et al., 1999; Longscope, 1996; Rosenfeld et al., 1971, 1975).

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Table 1
Summary of prior studies of sex differences in the relationship between DHEAS and health outcomes

Reference	Study type	Outcome	Relationship with DHEAS	
			Males	Females
Roth et al. (2002)	Longitudinal (25-year follow-up)	All-cause mortality	−	n/a
Mazat et al. (2001)	Longitudinal (9-year follow-up)	All-cause mortality	−	NS
Berr et al. (1996)	Longitudinal (4-year follow-up)	All-cause mortality	−	NS
Barrett-Connor et al. (1986)	Longitudinal (12-year follow-up)	All-cause, CVD, and IHD mortality	−	n/a
Trivedi and Khaw (2001)	Longitudinal (5- to 9-year follow-up)	All-cause and CVD mortality	−	NS
Mazat et al. (2001)	Longitudinal (7-year follow-up)	Change in self-rated health status	NS	NS
Berr et al. (1996)	Cross-sectional	Self-rated health status	+	NS
Mazat et al. (2001)	Cross-sectional	Mobility limitations	−	NS
Berr et al. (1996)	Cross-sectional	Mobility limitations	NS	NS
Ravaglia et al. (1996)	Cross-sectional	Limitations in activities of daily living (ADL)	−	NS
Barrett-Connor et al. (1999)	Cross-sectional	Beck depression inventory	n/a	−
Mazat et al. (2001)	Longitudinal (7-year follow-up)	Change in the CES-D	NS	NS
Berr et al. (1996)	Cross-sectional	CES-D	NS	−
Yaffe et al. (1998)	Cross-sectional	Geriatric depression scale (shortened)	n/a	−
Burkenhäger-Gillesse et al. (1994)	Cross-sectional	Alzheimer's disease	NS	NS
Mazat et al. (2001)	Longitudinal (7-year follow-up)	Change in Mini-Mental State Examination (cognitive function)	+	NS
Yaffe et al. (1998)	Cross-sectional	Mini-Mental State Examination	NS	NS
Ravaglia et al. (2002)	Cross-sectional	Dementia	−	NS
Tilvis et al. (1999)	Cross-sectional	Dementia	−	NS
Berr et al. (1996)	Longitudinal (4-year follow-up)	Dementia	NS	NS
Morrison et al. (2000)	Cross-sectional	Blessed memory information concentration test (cognitive impairment)	NS	+

CVD, cardiovascular disease; IHD, ischemic heart disease; CES-D, Center for Epidemiologic Studies Depression scale; n/a = not available (not included in the study); −, negative relationship; +, positive relationship; NS, no significant relationship.

subsequent mortality—particularly cardiovascular mortality—among men (Barrett-Connor et al., 1986; Roth et al., 2002), but little or no association among women (Berr et al., 1996; Mazat et al., 2001; Trivedi and Khaw, 2001).

Most studies of morbidity are based on cross-sectional data with two exceptions (noted below). One cross-sectional study finds low DHEAS associated with poor subjective health status among men but not women (Berr et al., 1996). Yet, a follow-up longitudinal study using the same dataset shows no such relationship for either sex (Mazat et al., 2001).

Similarly, there are mixed results regarding sex differences in DHEAS and physical functioning. As summarized in Table 1, two out of three studies find a significant relationship between DHEAS and physical functioning (e.g. mobility or ADL limitations) and in both cases, the association is significant only for men (Berr et al., 1996; Mazat et al., 2001; Ravaglia et al., 1996).

While these findings suggest that the relationship between DHEAS and various physical health outcomes is stronger for men than for women, other studies suggest that DHEAS may be linked with better psychological health for women but not men (Barrett-Connor et al., 1999; Berr et al., 1996; Yaffe et al., 1998). Nonetheless, the one longitudinal study found no significant relationship for either sex (Mazat et al., 2001).

Finally, previous research reveals inconsistent and contradictory results regarding the relationship between DHEAS and cognitive function. Although many studies find no relationship with various measures of cognitive function for either sex (Berr et al., 1996; Burkenhäger-Gillesse et al., 1994; Yaffe et al., 1998), three studies (one of which is longitudinal) report a link between DHEAS and cognitive function among men, but no difference among women (Mazat et al., 2001; Tilvis et al., 1999; Ravaglia et al., 2002). In contrast, Morrison et al. (2000) report a *positive* correlation between DHEAS and cognitive impairment among women. Yet, this study was based on a small ($n = 63$), highly select, convenience sample.

The mechanisms through which DHEA and DHEAS may affect health outcomes remain speculative. Research suggests that DHEA may act as a functional antagonist to the effects of glucocorticoids (Browne et al., 1993; Kalimi et al., 1994; Wolf and Kirschbaum, 1999), although it does not directly interact with the glucocorticoid receptor. Because chronically elevated cortisol levels are implicated in many conditions including heart disease, diabetes, and cognitive impairments (Lupien et al., 1999; Vanitallie, 2002), a counterbalancing action of DHEA might explain the relationship between DHEAS and such health outcomes. Some evidence also suggests there may be interactions of DHEA with neurotransmitter systems (e.g. serotonin),

which could account for the reported ability of DHEA administration in reducing depressive symptomatology (Abadie et al., 1993; Wolkowitz et al., 1997, 1999).

2. Material and methods

2.1. Data

The data were originally collected as part of the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan. This longitudinal survey began in 1989 with a national sample (including the institutionalized population) of 4049 persons aged 60 and older (response rate: 92%), and was expanded in 1996 to include 2462 near elderly persons aged 50–66 in 1996 (response rate: 81%) (Hermalin et al., 1989). Both groups of respondents were re-interviewed in 1999 (response rate: 90% of survivors from the original cohorts).

In 2000, a national sub-sample of respondents (among those interviewed in 1999) was selected randomly for the Social Environment and Biomarkers of Aging Study (SEBAS). Elderly respondents (71 and older in 2000) and residents of urban areas were oversampled. On a scheduled day, several weeks after an initial interview, participants collected a 12-h overnight urine sample, fasted overnight, and visited a nearby hospital the following morning for a physical examination. 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.

Among the 1713 respondents selected for the SEBAS, 1497 provided interviews (92% of survivors) and 1023 participated in the physical examination (68% of those interviewed); of the 474 who did not participate in the exam, 111 were not eligible because of a debilitating health condition and thus, were not asked to participate. Compliance with the clinical protocol was extremely high: almost all participants followed the urine protocol and provided a suitable blood sample. Seventeen participants were excluded from the analysis because a proxy completed the initial interview and 39 were excluded because of missing data on a dependent variable or covariate. Thus, the analysis sample includes 967 participants.

Restrictions based on health condition excluded a disproportionate number of the least healthy respondents, but those who reported themselves in 'excellent' health were also less likely to participate in the exam. While the analysis sample excludes respondents at both extremes of health, it nevertheless comprises sufficient variation to do multivariate analyses. Although respondents above age 70 were less likely than younger ones to participate in the clinical portion of the study, sex and various measures of socioeconomic status were not significantly related to participation. Because of higher non-participation rates of both the healthiest and the least healthy individuals, persons who received the medical exam reported the same general health status, on average, as those who did not. These results suggest that, in the presence of controls for age, estimates derived from the clinical information are unlikely to be seriously biased (Goldman et al., 2003a).

2.2. Measures

The dependent variables include measures of physical mobility, depressive symptoms, cognitive function, and self-assessed health status, all based on self-report in 2000. Mobility is based on questions about the respondent's ability to perform nine physical tasks: standing continuously for 15 min and for 2 h, 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 m), walking 200–300 m, and climbing two or three flights of stairs. The measure is a count of the number of tasks for which the respondent reports difficulty performing without aid.

Depressive symptoms are measured by a 10-item version of the original 20-item Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977). 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 (Boey, 1999) as well as other populations (Kohout et al., 1993; Rouch-Leroyer et al., 2000; Shrout and Yager, 1989; Turvey et al., 1999). The CES-D has also been used in other Chinese populations (Krause and Liang, 1992; Ofstedal et al., 1999). This short-form of the CES-D is coded according to standard practice yielding an index ranging from 0 to 30, with higher scores indicating more symptoms.

Cognitive function is based on 12 items from the modified Short Portable Mental Status Questionnaire (Pfeiffer, 1975), the modified Rey Auditory Verbal Learning Test (Lezak, 1983), and a modification of the Digits Backward test (Wechsler, 1981). For most items, one point is given if the respondent answers the question correctly. One task involves a series of four subtractions and one point is assigned for each correct subtraction (Herzog and Wallace, 1997). Another test involves the immediate recall of 10 nouns, with one point given for each noun recalled. Thus, the resulting measure ranges from 0 to 24. Following Herzog and Wallace (1997), a score of zero was assigned for each item the respondent refused to answer or said 'don't know.'

Self-assessed health status 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 'excellent' health. A wide literature has consistently shown this measure to be a strong predictor

of subsequent mortality and morbidity (Ferraro et al., 1997; Grand et al., 1988; Haga et al., 1995; Idler and Kasl, 1995; Jagger, Spiers, and Clarke, 1993; Kaplan et al., 1993; Møller et al., 1996; Mor et al., 1994; Shadboldt, 1997; for a review of 46 other studies see Idler and Benyamini, 1997; Benyamini and Idler, 1999). Therefore, this simple measure appears to be a valuable indicator of overall wellbeing.

The key independent variable is serum DHEAS, based on the fasting blood sample collected at the hospital (in 2000) and measured in micrograms per deciliter (μg/dl). Control variables include age, sex, smoking, alcohol consumption, and cortisol. Age is measured as of the date of the health exam based on birthdate. In order to obtain measures that predate the measures of DHEAS and health outcomes, reports of health behaviors are drawn from the 1999 interview. Smoking is measured by two variables: the number of years the respondent ever smoked (coded 0 if never smoked) and a dichotomous variable indicating whether she/he currently smokes. Alcohol consumption is represented by two dummy variables indicating whether the respondent never drinks alcohol and whether she/he drinks alcohol (nearly) everyday; the reference category includes those who drink alcohol once every 2 or 3 days or less often. Many studies have found smoking and alcohol consumption to be positively related to DHEAS (Barrett-Connor et al., 1986; Barrett-Connor and Goodman-Gruen, 1995; Kroboth et al., 1999; Poršová-Dutoit et al., 2000; Ravaglia et al., 2002; Trivedi and Khaw, 2001). The precise mechanism is unknown, but some researchers have speculated that the elevation of DHEAS may be a counter-reaction to the negative consequences of smoking (Poršová-Dutoit et al., 2000). Cortisol is based on the 12-h urine sample and measured in micrograms per gram creatinine to adjust for body size. Both cortisol and DHEA are secreted in response to adrenocorticotrophin (Kroboth et al., 1999).

Blood and urine samples were sent to Union Clinical Laboratories (UCL) in Taipei for measurements of DHEAS and cortisol. In addition to the routine standardization and calibration tests performed by the laboratory, duplicate samples for a 10% subset of the specimens were submitted to UCL and to Quest Diagnostics in the US for analysis. Data from these duplicates indicate high inter- and intra-lab reliability, with intraclass correlations of 0.80 or higher for duplicates sent to UCL and inter-lab correlations of 0.76 or higher between results from UCL versus Quest Diagnostics. DHEAS was measured by RIA (Dudley et al., 1985), with an inter-assay coefficient of variation (CV) = 12.9 and sensitivity = 1.1 μg/dl. HDL was measured by dextran sulfate (Ciba Corning Express 560), with CV = 4.7 and sensitivity = 7 mg/dl. Assays of urinary cortisol were made by high pressure liquid chromatography (Canalis et al., 1982; Krstulovic, 1983), with a lower detection limit of 4 μg/l.

2.3. Analytical strategy

Univariate and bivariate statistics are based on weighted data to compensate for oversampling by age group and urban residence. Multivariate models are based on unweighted data, but include age and a dummy variable for urban residence in order to account for oversampling. Because of the multistage sampling design, we use the robust estimator of variance to produce correct standard errors that adjust for clustering by primary sampling unit (StataCorp, 2001).

Mobility limitations are modeled using negative binomial regression because diagnostics indicate that this count variable is Poisson, but with extra variation (i.e. overdispersion). Thus, Poisson regression is not appropriate and tends to underestimate the standard errors (StataCorp, 2001). CES-D and cognitive function measures are modeled using linear regression. Because there is evidence of heteroskedasticity for both outcomes, we use a robust estimator of variance to calculate standard errors.[2] Finally, self-assessed health status (an ordered categorical variable) is modeled using ordered probit regression.

We estimate the models for each outcome in two stages. In the first model, we include only DHEAS, age, and sex. DHEAS levels have been shown to vary by age and sex (Orentreich et al., 1984; Šulcová et al., 1997), as does the prevalence of morbidity. Thus, we include these controls in order to identify the association with DHEAS independent of the effects of age and sex. Age is modeled as a quadratic if the squared term was significant ($p < 0.05$). All models include an interaction term between sex and DHEAS, and we tested sex interactions with all other covariates but retained only those interactions that were significant ($p < 0.05$).

In the second model, we add the remaining covariates (described above). The results from this model allow us to identify the relationship with DHEAS net of other covariates. For example, if smoking has the hypothesized positive effect on levels of DHEAS, then, because of the detrimental effects of smoking on health, failure to control for smoking in the model may act to suppress the hypothesized positive association between DHEAS and better health.

[2] We also tested alternative models such as taking the natural logarithm of the dependent variable. Because 24% of the sample had a score of 0 on the CES-D (for which the log is undefined), we added one to all the CES-D scores before taking the log. In the case of cognitive function, which has a negative skew, we reversed the scale to measure poor cognitive function (and added one to all scores) before taking the log. The log transformation makes the distributions more symmetric and the heteroskedasticity virtually disappears. Nonetheless, the substantive results are very similar to those obtained using the untransformed dependent variable with robust standard errors. Therefore, we present results based on the latter model because they are easier to interpret.

3. Results

Consistent with previous studies, these data indicate that the mean level of DHEAS tends to be higher among males than females. There is a pronounced decline with increasing age among males, but virtually no decline above age 60 for females (Fig. 1). Among those aged 54–59, the average level of DHEAS is 123 μg/dl for males compared with only 73 μg/dl for females. The comparable figures among those aged 80 and older are 63 μg/dl versus 58 μg/dl, respectively.

Descriptive statistics for all measures used in this study are presented in Table 2. The average number of mobility limitations within this sample is about two; the distribution is skewed. Forty percent of respondents have no mobility limitations, while 21% have more than three such limitations (data not shown). The average score on the CES-D is 5.5 (but 24% have a score of 0). Previous research suggests using 10 as the cutoff for clinical depression on the short-form CES-D (Andresen et al., 1994); 19% of this sample scored 10 or higher on the CESD. The mean score on the cognitive function index indicates that, on average, this population is able to correctly complete nearly 17 of 24 cognitive items. Finally, one-quarter of these older Taiwanese report themselves to be in 'good' or 'excellent' health, while 3% report 'poor' health and 23% say that their health is 'not so good'. Descriptive statistics for covariates are also shown in Table 2. For historical reasons, the percentage female is notably low (43%): in the late 1940s, there was substantial migration of Nationalists from Mainland China, most of whom were soldiers (and hence male).

The results from the multivariate models are presented in Table 3. To facilitate comparisons by sex, we show separate parameters for males and females (rather than a main effect and interaction effect) when there is a significant sex interaction. The coefficient shown for males (reference group) is equivalent to the main effect, while that for females equals the sum of the main and interaction effects.

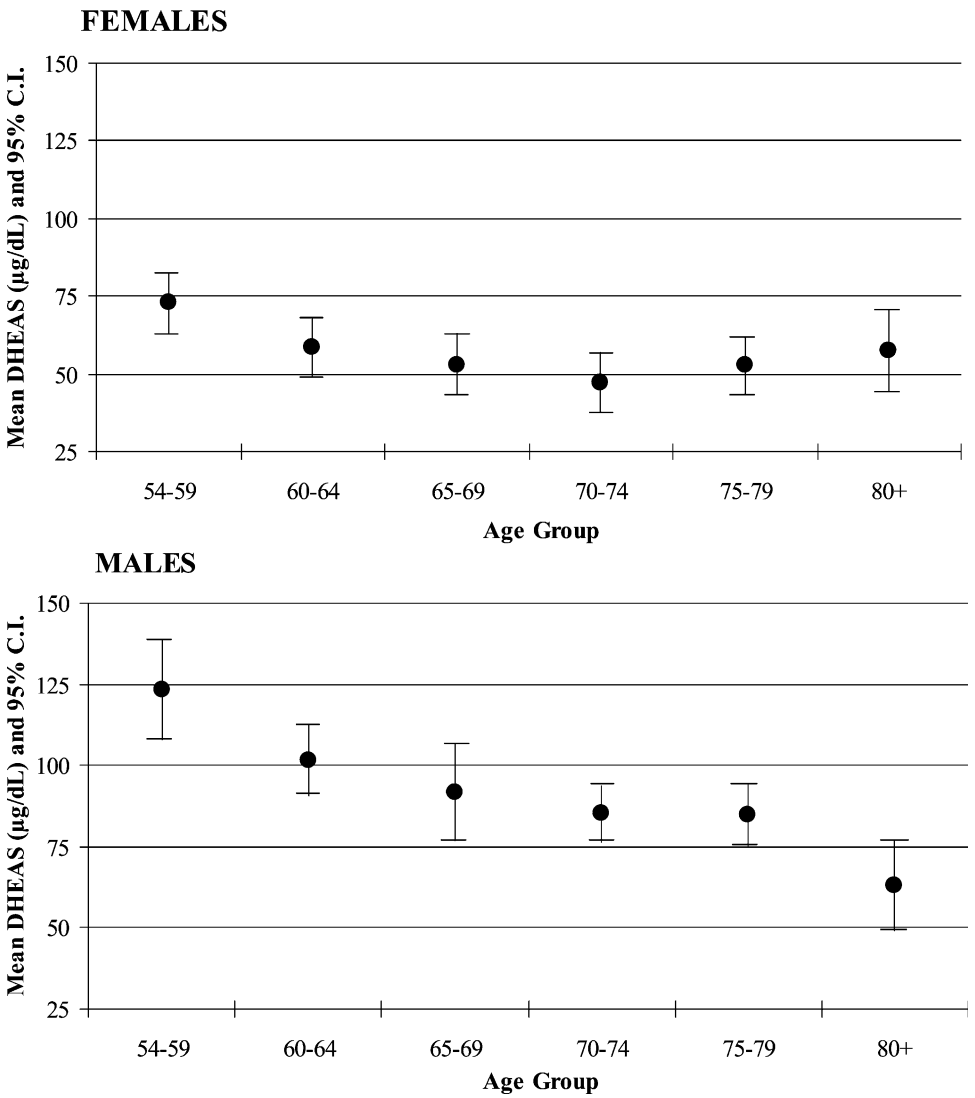

Fig. 1. Mean DHEAS and 95% confidence interval, by age group and sex, SEBAS 2000, weighted analyses.

Table 2
Descriptive statistics for all measures, SEBAS 2000, weighted analyses

Variable	Observed range	Mean or percentage	Standard deviation
Health outcomes			
Number of mobility limitations	0–9	1.88	2.28
CES-depression scale	0–28	5.46	5.38
Index of cognitive function	1–24	16.70	3.53
Self-assessed health status	1–5		
Poor (1)		3.2%	–
Not so good (2)		23.0%	–
Average (3)		24.8%	–
Good (4)		12.6%	–
Excellent (5)		12.4%	–
Covariates			
DHEAS (μg/dl)[a]	0–497	81.08	59.32
Age	54–91	66.32	8.01
Female	0,1	42.6%	–
Current smoker	0,1	26.6%	–
Number of years ever smoked	0–70	14.67	20.03
Alcohol consumption			
Never drinks	0,1	71.0%	–
Drinks ≤ once every 2–3 days	0,1	21.5%	–
Everyday or nearly everyday	0,1	7.5%	–
Cortisol (μg/g creatinine)	2–1291	28.42	57.59
Number of cases	967		

[a] 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 μg/dl) and could not be detected.

Table 3 indicates coefficients that are significantly different from zero as well as significant sex differences.

In order to demonstrate the magnitude of the relationship, we calculated predicted values for each of the health outcomes using the coefficients from Table 3. Using the analysis sample ($n = 967$), we recoded sex to the specified group, assigned DHEAS to the selected percentile value (i.e. 25th or 75th) based on the observed distribution for respondents of that sex, and retained all other explanatory variables at their observed values in the sample. For each outcome, the mean predicted value for the sample (assuming pre-selected values for sex and DHEAS) is shown in Table 4. Because the interquartile range for DHEAS is smaller among women than men, the associations among women are smaller than they would be if we used the percentile values for the overall sample.

The results demonstrate the expected negative association of DHEAS with mobility limitations (Tables 3 and 4). Even in the presence of other covariates (model 2), the association between DHEAS and mobility limitations remains significant and unattenuated, although much larger among women than men. Predicted values based on model 2 suggest that at the 25th percentile of DHEAS, women are predicted to have 3.1 mobility limitations compared with only 2.4 at the 75th percentile of DHEAS (Table 4). The difference between the corresponding values among men is 1.6 versus 1.4, respectively.[3] We also ran separate (logit) models for each type of mobility limitation (not shown) and found similar results: the association was always larger for women than for men, and in most cases, the relationship with DHEAS was significant for women, but not for men.

In contrast to the findings for mobility limitations, these data provide little evidence of a relationship between DHEAS and depressive symptoms. In model 1, DHEAS has a marginally significant (negative) association with the CES-D for females but not males (Table 3). Yet, once other covariates are added (model 2), the relationship is no longer even marginally significant among females.

The findings regarding cognitive function suggest a positive association with DHEAS among women, but not men. The magnitude is relatively small: based on model 2, females at the 25th percentile of DHEAS are predicted to correctly complete an average of 15.4 (of 24) cognitive items compared with 16.0 at the 75th percentile.

Finally, the estimates reveal a positive relationship between DHEAS and self-assessed health status, although it is significant only for men (likely due to the smaller sample size for women; the magnitude is identical). At the 25th percentile of DHEAS, one-quarter of males are predicted to report good or excellent health compared with 29% at the 75th percentile (Table 4, model 2). Though the magnitude of the coefficient is similar for females, the difference between predicted values at the 25th and 75th percentiles (20% versus 23%, respectively) is smaller due to the smaller inter-quartile range of DHEAS among women.

Our results indicate a significant independent association between cortisol and all outcomes except cognitive function (Table 3). Compared with DHEAS, cortisol has the reverse association with health: higher levels are related to more mobility limitations and depressive symptoms, and poorer self-rated health. Nonetheless, results not presented here reveal that the magnitude of the association is smaller than that of DHEAS. Based on a set of predicted values similar to those shown for DHEAS, women at the 25th percentile of cortisol (14.7 μg/g creatinine) are predicted to average 2.7 mobility limitations compared with 2.8 at the 75th percentile (34.5μg/u creatinine). Among men, and for other health outcomes, the association with cortisol is even smaller.

[3] We also have data on limitations in Activities of Daily Living (ADL), including six activities: bathing, dressing or undressing, getting out of bed or standing up, using the toilet, eating, and moving around the house. Nonetheless, so few respondents reported any difficulty with an ADL (only 3.4% reported at least one ADL limitation) that we have little statistical power. We estimated a similar model for number of ADL limitations and found that the coefficients for DHEAS were in the same direction as for mobility limitations, but none was significant.

Table 3
Coefficients from multivariate regression models of health outcomes on DHEAS and covariates, unweighted analyses

	Mobility limitations (negative binomial)		CES-D (linear)		Cognitive function (linear)		Self-assessed health status[a] (ordered probit)	
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)
DHEAS (μg/dl): Male[b]	−0.003** (0.001)	−0.003** (0.001)	−0.004 (0.002)	−0.003 (0.002)	0.000† (0.001)	−0.001† (0.001)	0.002** (0.001)	0.002** (0.001)
DHEAS (μg/dl): Female[b]	−0.005** (0.001)	−0.005** (0.001)	−0.017+(0.009)	−0.016 (0.009)	0.012**† (0.004)	0.012**† (0.004)	0.002 (0.001)	0.002 (0.001)
Female	0.698** (0.103)	0.632** (0.128)	2.181* (0.802)	2.081* (0.871)	−2.108** (0.507)	−2.237** (0.534)	−0.225+ (0.131)	−0.137 (0.179)
Age	0.051** (0.005)	0.048** (0.005)	0.049+(0.026)	0.056* (0.027)	−0.138** (0.018)	−0.135** (0.018)	−0.174** (0.057)	−0.183** (0.053)
Age-squared	–	–	–	–	–	–	0.001** (0.000)	0.001** (0.000)
Current smoker	–	−0.093 (0.159)	–	–	–	−0.446 (0.355)	–	–
Current smoker: Male[b]	–	–	–	1.381*+ (0.655)	–	–	–	0.186† (0.145)
Current smoker: Female[b]	–	–	–	6.624**† (2.180)	–	–	–	−1.021*† (0.406)
Years ever smoked	–	0.001 (0.003)	–	–	–	−0.002 (0.008)	–	–
Years ever smoked: Male[b]	–	–	–	−0.019† (0.016)	–	–	–	−0.001† (0.004)
Years ever smoked: Female[b]	–	–	–	−0.151**† (0.023)	–	–	–	0.018*† (0.007)
Never drinks alcohol	–	0.330** (0.116)	–	0.549 (0.424)	–	−0.479* (0.210)	–	−0.078 (0.098)
Drinks alcohol daily	–	−0.015 (0.167)	–	0.565 (0.600)	–	−0.145 (0.260)	–	0.054 (0.148)
Cortisol (μg/g creatinine)	–	0.002** (0.000)	–	0.007* (0.003)	–	−0.003 (0.002)	–	−0.001** (0.000)
Constant	−2.840** (0.357)	−2.960** (0.375)	2.212 (1.718)	0.990 (1.736)	25.818** (1.212)	26.274** (1.211)	–	–

Robust standard errors are shown in parentheses. Negative binomial regression is used to model mobility limitations. CES-D and cognitive function are modeled using linear regression. Ordered probit regression is used to model self-assessed health status. Models also include a dummy variable indicating urban residence. $^{+}$ $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; † Sex difference in the parameter estimate is significant at $p < 0.05$ level.

[a] The cutpoints for the ordered probit model 1 are −7.99, −6.78, −5.46, and −4.94. Those for model 2 are −8.30, −7.08, −5.74, and −5.23.

[b] 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).

Table 4
Predicted values for health outcomes for 25th and 75th percentile values of DHEAS

	Mobility limitations	CES-D	Cognitive function	Self-assessed health status				
				Poor	Not so good	Average	Good	Excellent
Model 1 (age and sex-adjusted)								
Females								
25th percentile (DHEAS = 28.7)	3.24	6.90	15.48	0.05	0.29	0.48	0.10	0.08
75th percentile (DHEAS = 78.0)	2.54**	6.05^{+}	16.09**	0.04	0.26	0.48	0.12	0.10
Males								
25th percentile (DHEAS = 53.7)	1.59	5.02	17.22	0.03	0.22	0.49	0.14	0.12
75th percentile (DHEAS = 125.4)	1.28**	4.76	17.19	0.02**	0.19**	0.48**	0.15**	0.15**
Model 2 (fully adjusted)								
Females								
25th percentile (DHEAS = 28.7)	3.06	6.13	15.44	0.05	0.27	0.47	0.11	0.09
75th percentile (DHEAS = 78.0)	2.39**	5.35	16.05**	0.04	0.25	0.47	0.12	0.11
Males								
25th percentile (DHEAS = 53.7)	1.63	5.02	17.27	0.03	0.23	0.49	0.13	0.12
75th percentile (DHEAS = 125.4)	1.36**	4.80	17.20	0.02**	0.20**	0.49**	0.15**	0.14**

Model 1 includes age and sex (in addition to DHEAS), while model 2 includes all covariates shown in Table 3. Predicted values are calculated by setting sex and DHEAS to the specified values, while leaving all other covariates at their observed values in the sample; the values shown represent the mean predicted values for the sample assuming the specified sex and level of DHEAS. $^{+}$ $p < 0.10$; * $p < 0.05$; ** $p < 0.01$ (for difference by DHEAS level).

Because DHEAS and cortisol are thought to act in opposing ways, some argue that the ratio of cortisol to DHEAS is a better measure of hypercortisolaemia than cortisol alone (Goodyer et al., 1998). We estimated an auxiliary set of models where we substituted the ratio of cortisol to DHEAS for individual measures of DHEAS and cortisol. The results (not shown) indicate that although the ratio is often statistically significant, the magnitude of the relationship is much smaller than for DHEAS alone. The biggest association is for self-assessed health among males: at the 25th percentile of cortisol/DHEAS, 30% are predicted to be in good or excellent health compared to 28% at the 75th percentile (corresponding figures for DHEAS: 25% versus 29%).

4. Discussion

Comparisons of DHEAS levels in this study with those from other samples are problematic because differences may result from variation in how the samples are defined. Although we have not found any other reports of DHEAS levels for a nationally representative sample, data from various community-based samples suggest that comparisons between Taiwan and other countries differ depending on sex, age, and the sample itself. Data from the MacArthur Study of Aging, a sample of high-functioning elderly (aged 70–79) in three US communities, suggests that median levels of DHEAS are comparable to those of the Taiwanese elderly cohort (Goldman et al., 2003b). Studies based on a sample of whites in a US community show mean DHEAS levels that are somewhat higher than in the Taiwan sample, particularly for men (e.g. among those aged 60–64, 152 μg/dl versus 102 in Taiwan) and at ages less than 80 (Barrett-Connor et al., 1986, 1995, 1999). Yet, another population-based sample of white women in three US cities indicates mean levels that are lower than in Taiwan, a gap that increases at older ages; for example, among those aged 80 and older, the mean was 30 μg/dl versus 58 in Taiwan (Yaffe et al., 1998). Two studies based on an elderly sample from a community in France report levels of DHEAS that are similar to Taiwan, although again levels among women aged 80 and older tend to be lower than in Taiwan (Berr et al., 1996; Mazat et al., 2001). A community-based sample of elderly in Italy reveals levels of DHEAS (by sex) that are similar to age-comparable Taiwanese (Ravaglia et al., 2002), while a study of three elderly birth cohorts in Helsinki, Finland, exhibits levels that appear to be higher than in Taiwan (Tilvis et al., 1999). Thus, it is difficult to draw conclusions about whether population levels of DHEAS differ between Taiwanese and other groups.

As summarized in Table 5, the findings regarding the relationship between DHEAS and health outcomes differ from previous studies. Whereas we find a stronger relationship with physical functioning among women than men, previous studies based on samples of the elderly population in France (Mazet et al., 2001) and Italy (Ravaglia et al., 1996) showed an association only among men (not women). On the other hand, we find little evidence that DHEAS is related to depressive symptoms among either sex, whereas several other studies in the US and France demonstrated a negative relationship for women (Barrett-Connor et al., 1999; Berr et al., 1996; Yaffe et al., 1998). Finally, previous studies have often

Table 5
Summary of results regarding the relationship between DHEAS and health outcomes

Relationship with DHEAS	Functional limitations	Depressive symptoms	Cognitive function	Self-assessed health status
This study[a]				
Males	−	NS	NS	+
Females	−	NS	+	NS
Previous studies[b]				
Males	− in 2 of 3 studies	NS in 2 of 2 studies	+ in 3 of 7 studies	+ in 1 of 2 studies
Females	NS in 3 of 3 studies	− in 3 of 4 studies	− in 1 of 7 studies	NS in 2 of 2 studies

− , Negative relationship; +, positive relationship; NS, no significant relationship.
[a] Based on fully adjusted model (Table 3, model 2).
[b] See Table 1 for details.

found no association with cognitive function among either sex and when they did find a relationship, it was usually only among males. In contrast, our results regarding cognitive function indicate a positive (albeit substantively small) relationship for women (but not men).

One hypothesis for why our results with respect to depression may differ from those in Western countries pertains to diet (V. Papadopoulos, personal communication, July 22, 2003). Because DHEA serves as a precursor to androgens and estrogens (Labrie, 1991; Labrie et al., 2001), the effects of DHEA(S) may be attributable to their conversion into these other hormones. Soy-based nutrition contains high levels of estrogenic compounds (e.g. genistein), and thus, may serve as an alternative or additional source of estrogen. Nagata et al. (2000) found that both DHEAS and a soy diet were inversely correlated with the CES-D, resulting perhaps from the effects of increased estrogen levels on psychological well-being. If the Taiwanese diet is higher in genistein than the Mediterranean diet, then the effects of DHEAS-derived estrogen may be less important in Taiwan than in Western countries because the soy-based diet provides an alternative source of estrogen.

The reasons for other differences between this study and those conducted elsewhere are not clear. Differences in the social and cultural environment between Taiwan and Western countries could provide an explanation, but we have no information on how environmental factors may interact with DHEAS in their effects on health.

The cross-sectional design of this study is a major limitation. In the absence of longitudinal data on subsequent health outcomes, we cannot establish causal direction. While DHEAS may be protective of health, by reducing the risk of subsequent morbidity, the relationship may also work in the opposite direction: low levels of DHEAS may be a consequence of ill health. In one study that controlled for the presence of diseases, researchers found no relationship between DHEAS and all-cause or cardiovascular mortality among men or women (Tilvis et al., 1999). If a decreased DHEAS level is a result of disease, its relationship with mortality may be spurious. However, if declining DHEAS precipitates illness, then it may result in greater mortality via its contribution to morbidity. Unfortunately, these cross-sectional data do not allow us to distinguish a spurious from a mediating relationship. A followup of this survey conducted in 2003 will provide data on subsequent health outcomes that will permit us to begin to untangle these mechanisms.

A better understanding of the direction of causation may have important implications for DHEA supplementation. In 1985, the FDA banned the sale of DHEA, but it re-emerged as a 'dietary supplement' with the passage of the Dietary Supplement Health and Education Act of 1994. It is now widely available—and by some accounts among the most popular of supplements—with great claims being made for its benefits.[4] Yet, if low DHEAS is a result of illness rather than a precursor to poor health, it seems unlikely that DHEA supplementation would have protective benefits. Whether DHEA represents a fountain of youth (Baulieu et al., 2000) remains unknown, but research that identifies the physiological pathways linking various biomarkers and health outcomes could provide crucial evidence to answer this question.

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[4] DHEA supplementation has been shown to increase levels of both DHEA and DHEAS, and is thought to be more reliable and effective than DHEAS supplementation (Shealy, 1995). Although there is evidence that DHEA is metabolized into DHEAS (Arlt et al., 1998; 1999), it is possible that DHEA supplementation may not have the same effect as endogenous DHEAS.

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