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Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: A French community-based study

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ABSTRACT **In human beings of both sexes, dehydroepiandrosterone sulfate (DHEAS) circulating in blood is mostly an adrenally secreted steroid whose serum concentration (in the micromolar range and 30–50% higher in men than in women) decreases with age, toward ≈20–10% of its value in young adults during the 8th and 9th decades. The mechanism of action of DHEA and DHEAS is poorly known and may include partial transformation into sex steroids, increase of bioavailable insulin-like growth factor I, and effects on neurotransmitter receptors. Whether there is a cause-to-effect relationship between the decreasing levels of DHEAS with age and physiological and pathological manifestations of aging is still undecided, but this is of obvious theoretical and practical interest in view of the easy restoration by DHEA administration. Here we report on 622 subjects over 65 years of age, studied for the 4 years since DHEAS baseline values had been obtained, in the frame of the PAQUID program, analyzing the functional, psychological, and mental status of a community-based population in the south-west of France. We confirm the continuing decrease of DHEAS serum concentration with age, more in men than in women, even if men retain higher levels. Significantly lower values of baseline DHEAS were recorded in women in cases of functional limitation (Instrumental Activities of Daily Living), confinement, dyspnea, depressive symptomatology, poor subjective perception of health and life satisfaction, and usage of various medications. In men, there was a trend for the same correlations, even though not statistically significant in most categories. No differences in DHEAS levels were found in cases of incident dementia in the following 4 years. In men (but not in women), lower DHEAS was significantly associated with increased short-term mortality at 2 and 4 years after baseline measurement. These results, statistically established by taking into account corrections for age, sex, and health indicators, suggest the need for further careful trials of the administration of replacement doses of DHEA in aging humans. Indeed, the first noted results of such "treatment" are consistent with correlations observed here between functional and psychological status and endogenous steroid serum concentrations.**

Dehydroepiandrosterone sulfate (DHEAS) is secreted by the adrenal cortex (1), and its serum level in human beings is the highest of all steroids. Its long half-life (≈8–10 hr), limited diurnal variations, and lack of noticeable changes of metabolism in aging make the serum level a convenient marker of its adrenal production (2). However, the physiological function of DHEAS is far from being well known. It is reversibly synthesized from and hydrolyzed to the corresponding free steroid DHEA (also secreted by the adrenals), which itself can be partially metabolized into active androgens and estrogens in peripheral tissues (1–5). However, the physiological significance of this conversion to potent sex hormones is still not understood, even though it may be important pathologically. A remarkable feature of DHEAS levels in both men and women is their decrease with age, as indicated by several cross-sectional studies; after maximum levels are reached during the 3rd decade of life, there is a progressive decline with age so that DHEAS levels remain 20% or less of the maximum concentration in the serum, after 70 years of age (6–14). The progressive decline of DHEA(S)‖ is not the only hormonal decrease and, in particular, while the serum cortisol concentration is maintained there is most often a profound decrease of serum growth hormone and insulin-like growth factor 1 (IGF-1).

The decline of DHEAS with age has led to considering the intriguing possibility that its serum levels are related to the development of age-associated "normal" changes, as well as diseases such as cancer, atherosclerosis, or Alzheimer disease (14–22). Results to date have not been conclusive. No evidence for a relationship with cognitive disorders in the elderly has been found in one community-based study (23). In the same population, the relationship between low levels of DHEA at baseline and the cardiovascular causes of long-term mortality in men has been studied with controversial results (14, 23–25). No relationship was observed in women (24, 26).

Two research strategies may help to define a possible role for DHEA(S) in the aging process. The first strategy is to correlate endogenous DHEA(S) levels with physical and mental health parameters in population-based studies rather than to persons already sick. Such epidemiological studies try to relate DHEAS levels [it is easier and safer to measure than DHEA (see ref. 27)] to a number of health parameters and subsequent events, including death. The second approach is to administer DHEA, largely transformed to DHEAS in the body (1–5), and to observe any resulting changes within various health parameters. In a recent paper (28), the effects of a replacement dose of DHEA (50 mg administered orally for 3 months), were observed in 30 individuals, 40–70 years of age. Besides restoration of DHEA and DHEAS levels to "young" levels, there

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Abbreviations: DHEAS, dehydroepiandrosterone sulfate; MMSE, mini mental state examination; IGF-1, insulin-like growth factor 1; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living.

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‖In this paper DHEA(S) stands for the sum of DHEA plus DHEAS (interconvertible steroids). The form of the sulfate concentration is greater than or equal to two orders of magnitude larger than that of DHEA. Practically, DHEAS and DHEA(S) measurements give the same results.

was an increase of bioavailable IGF-1 in the blood associated with a remarkable augmentation in perceived physical and psychological well-being in both men and women.

In this work, referring to the first strategy, we measured the baseline DHEA(S) levels in the serum of individuals more than 65 years of age, studied for ≈5 years in the PAQUID** program, a longitudinal community-based study of the elderly (29) designed to investigate possible correlations with functional, psychological, and mental status, and therefore to see if the results are consistent with the preliminary reported effects of replacement doses of administered DHEA. Furthermore, after 2- and 4-year follow-ups, we could also assess incident dementia and mortality.

METHODS

Population. The PAQUID research program is a prospective cohort study of mental and physical aging in a representative sample of elderly subjects residing in south-west France (the Gironde "Département"). Three criteria had to be met for subjects to be included in the study: (*i*) to be at least 65 years of age on December 31, 1987; (*ii*) to live at home at the time of the initial data collection; and (*iii*) to be included on the communal (local) electoral lists. The general methodology of PAQUID has been described elsewhere (29). In brief, in 1988, all subjects were interviewed for one and one-half hours at home by a trained psychologist. The baseline data collected included socio-demographic items, assessment of functional disability and health status, and current medication. In addition, a set of psychometric tests assessing cognitive functioning and depressive symptomatology was given.

The educational level of participants was divided into three categories: (*i*) no schooling, (*ii*) primary without or with a degree, and (*iii*) secondary/baccalaureate/university.

Of the 2792 subjects living in Gironde included at baseline in the PAQUID cohort, we studied 622 volunteers who agreed to have blood sampling at home. Samples were collected between January 1990 and March 1991, close to the first follow-up examination (1 year after inclusion). These 622 subjects were compared with other subjects of the cohort. This sub-group did not differ from the others with respect to sex, but they were slightly younger (74.8 vs. 76.2 years, $P < 0.001$) and had a higher educational achievement (41.7% vs. 34.6%, $P = 0.003$). There were no more complaints with respect to subjectively perceived health (40.5% vs. 43.9%, $P = 0.2$), but these subjects were less dependent than the others, according to the Instrumental Activities of Daily Living (IADL) criteria (23.1% vs. 31.5%, $P < 0.001$). A similar percentage of depressive symptomatology was recorded (10%).

Functional, Psychological (or Well Being), and Mental Status. Physical functional disability was measured on the Activities of Daily Living (ADL) scale (30). Subjects who needed help for at least one of the six activities assessed by the ADL scale were classified as "dependent." Functional assessment also included the eight items of the IADL scale of Lawton and Brody (31), for which subjects were categorized according to the number of limitations (dependence was defined for at least one limitation). Mobility was described by a six-level scale (32): being confined to bed, being confined to home, moving restricted to neighborhood or district, difficulties in using means of transportation, no restriction in movement. Confinement was defined as the subject being limited to home or bed. In this survey, dyspnea, which is closely associated with dependence and loss of mobility (33), was defined according to the following question: Do you feel out of breath in some of the following circumstances; never (level 1), during a major effort such as climbing one flight of stairs (level 2), during a minor effort such as walking with other people of your own age on a level surface at a normal pace (level 3), during every day activities such as dressing or undressing (level 4), or confined to bed (level 5). Subjects who gave a positive response for levels 3, 4, or 5 were classified as dyspnoeic as defined by Vestbo *et al.* (34).

Global self-perceived health was assessed with the following formulation: Do you presently rate your health status very good, good, fair, bad, or very bad? For subjective health, subjects were considered in poor condition if they rated themselves as fair, bad, or very bad. On a scale of 1 to 7, each subject was asked to assess their life in general, with 1 being not at all satisfied and 7 totally satisfied. Subjects were considered as dissatisfied with life if their scores were 1, 2, 3, or 4. Depressive symptomatology was measured by the 20-item Center for Epidemiologic Studies–Depression (CES-D) scale (35), with scores ranging from 0 to 60. Scores higher than 16 in men and 22 in women were considered as indicative of depression.

The Folstein Mini Mental State Examination (MMSE) was used to provide a global measure of cognitive functioning, with scores ranging from 0 to 30. This test is frequently used for screening for dementia in epidemiological studies; an MMSE score under 24 suggests possible cognitive impairment (36, 37). The test battery also included evaluation of visual memory (Benton's Visual Retention test), verbal memory (Weschler's Paired Associates test), verbal fluency (Isaac Set test), visuospatial attention (Zazzo's test), simple logical reasoning (Weschler's Digit test), and abstractional abilities (Similarities Test of the Weschler's memory scale). In each of these tests, a high score corresponds to good cognitive performance. For each test, the percentile distribution of the scores was determined, and we classified the cognitive performance of each subject into two classes according to their place above or below the 25th percentile.

After the psychometric evaluation, the psychologists systematically completed a standardized questionnaire to obtain a clinical diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSMIII-R) criteria for dementia (38). In the second stage, subjects who met these criteria were seen by a neurologist who completed the examination according to the DSMIII-R criteria (39), conducted tests according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders criteria (40), and obtained the Hachinski score (41) to specify the etiology.

Follow-Up. Subjects were revaluated 1, 3, and 5 years after the baseline visit (2 and 4 years after blood sampling), following the same procedure as for the baseline visit.

Events of interest for this report were incident dementia and death.

Two years after blood sampling, 26 subjects were dead (4.2%), one subject was lost to follow-up, and 67 (10.8%) refused the follow-up procedure. Four years after blood sampling, these numbers were 89 (14.3%), 5 (0.8%), and 64 (10.3%), respectively. For subjects who died during the follow-up (45 men and 44 women), the cause of death was investigated with the help of the subject's general practitioner. Causes of death were obtained for 83 subjects (93%) and coded for using the ninth revision of the International Classification of Disease. Cardiovascular disease (including ischemic heart, vascular, and cerebrovascular diseases) was diagnosed for 44 subjects (24 men and 20 women). Cancers represented the second major cause of death in this sample with 18 cases (8 men and 10 women).

Serum DHEAS Measurements. All blood samples were kept frozen in liquid nitrogen until studied in 1994. DHEAS serum concentrations were measured directly in serum by an automated immunoenzymatic assay, on the Serono SR1 analyzer.

**PAQUID: Personnes Agées Quid; i.e., People (personnes) Aged (âgées) what about (Quid, in Latin).

Correlation with standard radioimmunoassay (42) was assessed ($r = 0.98$). The lower detection limit of the assay was 16 ng/ml. The intraassay coefficient of variation was 6%. The interassay coefficient of variation ranged from 3% (concentrations lower than 100 ng/ml) to 20% (concentrations higher than 1000 ng/ml).

Statistical Analysis. Analysis was conducted using the BMDP statistical software. Means (m) of DHEAS are given with standard deviations (SD). Because of the skewed distribution of DHEAS, logarithmic transformation was performed to normalize the observations (43).

Relationships between DHEAS and categorical variables were examined by ANOVA, single factor or multifactorial, when controlling for age. Furthermore, we performed forward multiple regression analysis ($P < 0.05$ to enter in the model) to examine the independent effect of health measures associated with DHEA levels. The model included demographic factors and all factors that were found to be associated with DHEA levels in men or women ($P < 0.05$). The association with mortality was also studied with a forward multiple regression model including all factors previously selected.

RESULTS

In the population studied, the mean plasma level of DHEAS was equal to 662 ng/ml (SD = 500) with a range from 49 to 3660 ng/ml. For the total group, serum DHEAS decreased from 742 ng/ml, the mean for subjects below 75 years of age to 589 ng/ml, the mean for subjects above 90 years. Concentrations were not distributed normally, but were skewed to the higher values. For statistical analysis, tests were performed on the log values of DHEAS levels. The level for the 266 men (m = 835 ng/ml, SD = 579) was significantly higher than the level of the 356 women (m = 532 ng/ml, SD = 385, $P < 0.0001$).

Table 1 shows DHEAS levels in four age groups. In men we observed a decrease of DHEAS levels from 1006 ng/ml for subjects below 70 years of age to 696 ng/ml for subjects above 80 years of age ($P = 0.06$). The DHEAS level was higher in the youngest women ($P = 0.03$). In each age class, levels for men were significantly higher than those for women. In neither men nor women, was there a significative difference in DHEAS levels according to education (Table 1).

Associations with Functional, Psychological, and Mental Status. Controlling for age, levels of DHEAS were significantly lower in women who had IADL limitation, who were confined to bed or home, or who presented dyspnea (Table 2). Such a decrease was also observed when women scored themselves in poor health or with no life satisfaction. As assessed with the CES-D scale, the presence of depressive symptomatology was associated with low levels of DHEAS.

Conversely, for men, lower levels of DHEAS were only significantly correlated to self-appreciate poor health, but not to other items whose results however point clearly to the same differences as in women. In a recently published study on healthy, free-living, over 90 year olds, there is correlation between the highest DHEA levels and ADL in men (44).

In men and women, there was a significant age-adjusted association with the number of medical drugs taken. There was thus a correlation between decreased DHEAS levels and the increased number of medical drugs taken.

MMSE taken as a global cognitive measurement did not give a clearcut conclusion on the mental status vs. DHEAS levels. Those levels were slightly lower in men who had an MMSE score under the 25th percentile compared with all others (721 ng/ml vs. 889 ng/ml), but the difference was not statistically significant after controlling for age. In women, DHEAS levels were the same for subjects with MMSE <25 (553 ng/ml) and for all others (533 ng/ml). For the five other tests studied (data not shown), only one significant association was observed: DHEAS levels were lower for women who scored under the 25th percentile for the Benton Visual Retention Test (483 ng/ml vs. 576 ng/ml, $P < 0.05$), but this difference was not observed for men (840 ng/ml vs. 861 ng/ml, ns). Cognitive scores were not further considered in this analysis. Prevalent cases of dementia ($n = 26$) had the same DHEAS levels as other subjects.

Using forward multiple regression analysis, we examined the independent relationship between various factors and DHEAS levels in a model including age and all factors found to be associated ($P < 0.05$) to DHEAS levels in men or women (age, IADL dependence, mobility, dyspnea, depressive symptomatology, subjective health, life satisfaction, and number of medications). This model was performed for each gender and on the whole sample, including sex as a covariate (Table 3).

In men the decrease with age was significant, and we confirmed the relationship between low levels of DHEAS and self-appreciated poor health. For women the effect of age was not significant, and three factors remained associated with low levels of DHEAS: IADL dependence, depressive symptomatology, and dyspnea. On the whole population sample, sex difference and age effect remained highly significant, as well as the negative association of DHEAS levels with two parameters, poor subjective health and dyspnea.

Follow-Up at 2 and 4 Years. Fourteen cases of dementia were registered during the follow-up after 2 years, 23 cases

Table 1. Mean levels of DHEAS according to age and educational levels in the PAQUID study, by sex

	Men		Women	
Age and education level	No.	Mean levels, ng/ml	No.	Mean levels, ng/ml
Age group, years				
66–69	83	1006 ± 705	100	644 ± 449
70–74	60	821 ± 549	67	491 ± 251
75–79	77	745 ± 508	93	502 ± 374
≥80	46	696 ± 390	96	474 ± 381
Whole population		835 ± 579		532 ± 385
Education				
No schooling	6	580 ± 244	15	513 ± 350
Primary with or without degree	137	771 ± 546	209	523 ± 362
Secondary/university	123	920 ± 616	132	550 ± 424

Number of men studied 266, women 356.
ANOVA shows a significant difference between men and women ($P < 0.001$) and for the four age classes in women ($P = 0.03$), but not for men ($P = 0.06$). Mean levels ± SD.

Table 2. Mean levels of DHEAS according to functional and mental status and psychological well-being

Status	Men		Women	
	No.	Mean levels, ng/ml	No.	Mean levels, ng/ml
ADL				
No limitation	226	847 ± 568	287	535 ± 374
Limitation	25	936 ± 680	48	565 ± 489
IADL				
No limitation	212	884 ± 587	240	570 ± 393**
Limitation	40	699 ± 505	96	458 ± 374
Mobility				
No confinement	245	861 ± 575	317	548 ± 388*
Confined bed or home	8	595 ± 660	25	409 ± 390
Dyspnea				
No	207	886 ± 605	235	583 ± 396***
Yes	42	674 ± 351	98	447 ± 366
Depressive symptomatology				
No	231	857 ± 586	283	561 ± 394***
Yes	16	802 ± 505	36	362 ± 271
Subjective health				
Good	162	913 ± 547*	192	577 ± 401*
Poor	91	744 ± 620	150	488 ± 369
Life satisfaction				
Yes	181	886 ± 622	213	580 ± 395*
No	57	729 ± 431	107	469 ± 359
No. of medications				
0–1	54	1106 ± 702*	45	536 ± 357*
2–4	99	820 ± 530	137	615 ± 426
5 or more	96	751 ± 519	151	480 ± 359

Number of men studied 266, women 356. Mean levels ± SD. Analyses were performed separately in men and women for each item. *P* values are given controlling for age: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

after 4 years. There was no association between the levels of DHEA and incidence of dementia in either men or women.

Vital status was ascertained 2 and 4 years after blood sampling, and we recorded 26 deaths and 89 deaths, respectively, at these two end points. In men, subjects who died during the 2- and 4-year intervals had the lowest DHEAS levels and this remained significant when controlling for the effect of age ($P < 0.001$, Table 4). The same death rate was observed in women after 2 or 4 years, whatever the DHEAS level.

Thus, for men, we examined relationships between DHEA and mortality using a multiple regression model including mortality and all the variants presented in Table 3 (age, IADL dependence, mobility, dyspnea, depressive symptomatology, subjective health, and number of medications). When controlling for these factors, which are known to be associated to various degrees with mortality, the relationship between DHEAS and mortality of men remained significant after 2 and 4 years.

For men (Table 4), we examined levels of DHEAS in terms of cause of death, and classified these causes in three groups: cancer, cardiovascular diagnosis, and other. The eight men who developed cancer had rather low levels of DHEAS, and we also observed low baseline values for the 24 men who died from cardiovascular diseases, as compared with other causes. However, these differences were observed in small groups and were not statistically significant. In women, no trend appeared between the three groups of causes of death.

DISCUSSION

This report studied community dwellers more than 65 years old, in their natural environment, and whenever possible leading a "normal life," of the possible correlations between their blood DHEAS levels and the baseline characteristics of their functional, psychological, and mental status. Moreover, a relationship could also be examined with incident cases of dementia and short-term longevity in the 4 succeeding years.

The number of significant results found is of some interest, since it is consistent with the concept we favor of DHEAS being an individual marker (42), probably in part genetically determined (45). These results confirm the persistence of the difference between DHEAS serum concentrations of men and

Table 3. Multiple regression analyses (forward)

Variants	Whole sample	Men	Women
Sex	−0.42 [−0.56, −0.29]***	—	—
Age	−0.02 [−0.03, −0.01]**	−0.02 [−0.01, −0.002]*	NE
IADL dependence	NE	NE	−0.24 [−0.44, −0.03]*
Dyspnea	−0.24 [−0.40, −0.08]**	NE	−0.29 [−0.48, −0.09]*
Depressive symptomatology	NE	NE	−0.38 [−0.65, −0.1]**
Subjective health	−0.21 [−0.35, −0.08]**	−0.32 [−0.53, −0.11]**	NE

DHEAS levels and factors associated on the whole sample and for each gender. Coefficient of regression (β is presented with its 95% confidence interval). NE, variable not entered in the model ($P > 0.05$). Three variables (life satisfaction, mobility, number of medications) did not reach statistical significance for the three models presented. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

Table 4. DHEAS levels according to mortality after 2 and 4 years

Mortality	Men No.	Men Mean levels, ng/ml	Women No.	Women Mean levels, ng/ml
Vital status at 2 years				
Alive	256	854 ± 579***	340	525 ± 371
Dead	10	332 ± 298	16	685 ± 609
Vital status at 4 years				
Alive	221	875 ± 583***	312	524 ± 374
Dead	45	638 ± 525	44	589 ± 450
Cause of death				
Cancer	8	339 ± 207	10	492 ± 234
Cardiovascular disease	24	645 ± 431	20	609 ± 500
Other	12	772 ± 753	9	567 ± 613

Number of men studied 266, women 356. Analyses were performed separately in men and women for each item. P values are given controlling for age: ***, $P < 0.001$.

women after 65 years of age, even if the decrease with age continues to be significant in men but not in women, after correcting for health indicators. We are currently measuring DHEAS in the serum of ≈400 of the original 622 people reported here, and will then obtain a longitudinal picture of the DHEAS decrease with age, which may vary considerably according to the individuals (46).

Results concerning functional dependence in our study go in the same direction as those previously observed in men and women taken together, such as in the Established Populations for the Epidemiologic Study of the Elderly study (47) and two other more limited studies (44, 48). A successful open study of the administration of DHEA to depressed people has been presented (49).

Correlations between DHEAS levels and the varied indices of functional and psychological status differ in men and women; women having many more health parameters statistically associated with the steroid levels than men. The two groups were very similar, although there were more women and they were slightly older. The statistical analysis of associations between DHEAS and health indicators is more powerful in women, and that may explain why many more statistical differences can be found in women. However, the preliminary numbers indicate that the results always evolve in the same direction for both sexes. Because women express their problems more openly, the difference between men and women may be artificial and due to the type of investigations used. Alternatively, gender differences may exist biologically, and DHEAS may play a distinct role in the sexes for hormonal reasons (incidently only four women were under estrogen replacement therapy at the time of the study).

Correlations between lower DHEAS concentrations and functional impairment, dyspnea, depressive symptomatology, poorer indices of well being, and the use of more medications are difficult to explain in terms of a mechanism of action and a cause-and-effect relationship. Mechanisms through which DHEAS may be active involve its partial transformation into active sex steroids, androgens, and/or estrogens in many tissues. A modulatory effect on the availability of IGF-1, which itself has many target tissues, could also be implicated. An increase of circulating IGF-1 has been observed after DHEA administration (ref. 28 and unpublished results), and we are studying correlations between DHEAS and IGF-1 in our aging subjects (A. Raynaud-Simon and Y. Le Bouc, unpublished work). A number of biological items have been suggested to be related to DHEA(S) levels, such as immunological activities, control of superoxidation, etc. (27). However, the global function of DHEAS remains poorly explained, and in any case DHEAS levels probably interfere with other hormonal components, including the decreasing growth hormone, increasing insulin, changed in sex hormones, etc.

No relationship between global cognitive function and dementia occurring in the 4 years following DHEAS measurement has been observed. Incidently, we did not find that subjects with prevalent dementia or Alzheimer disease had lower DHEAS levels than other subjects in good health (22).

Until now, only one population-based study has envisaged the relationship between DHEAS level and mortality (15). However, the correlation between low DHEAS and mortality is not found in all published analyses according to the length of the period of survey, the sex of the subjects, the cause of death (cardiovascular vs. all others), and considered factors (age, cardiovascular risk factors) (15, 23–26). Two studies of relatively short-term mortality (≤3 years) on smaller populations did not give association (22, 48). In our study, a significant correlation was established involving age and health indicators, between lower DHEAS levels and mortality in men after 2 or 4 years. However, the number of cases is rather low, and we could not perform separate analyses for each group; this will follow after further studies. Cases of cancer were relatively infrequent, and the major causes of death were of a cardiovascular nature, as in the early results of Barrett-Connor *et al.* (15). The biological meaning of the correlation below low DHEAS values in aging with mortality remains unexplained. One possibility is that a low DHEAS concentration is consequential to an as yet undetected fatal disease [as has been suggested for the association between low cholesterol and increased mortality (50)]. After all, low cholesterol and low DHEAS may be themselves correlated in spite of results to the contrary (48). Conversely, do low DHEAS levels negatively influence important vital processes? Is the lack of correlation in women a statistical artefact or is there a different DHEAS-related physiology in women?

In any case, observations over a longer time and with larger samples of aging people are necessary to establish a definitive statistical relationship between DHEAS and longevity (previously discussed; see refs. 27 and 42). We are far from having obtained a predictive index, but the present data do favor performing more studies of the possible beneficial effects of DHEA administration, particularly with low, replacement doses that do not lead to undesirable high levels of active sex steroids (27).

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