

Trajectories of Dehydroepiandrosterone Sulfate Predict Mortality in Older Adults: The Cardiovascular Health Study

Anne R. Cappola,¹ Ellen S. O'Meara,² Wensheng Guo,³ Traci M. Bartz,²
Linda P. Fried,⁴ and Anne B. Newman⁵

¹Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia.

²Department of Biostatistics, University of Washington, Seattle.

³Division of Biostatistics, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia.

⁴Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York.

⁵Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pennsylvania.

Background. Dehydroepiandrosterone sulfate (DHEAS) has been proposed as an antiaging hormone, but its importance is unclear. Assessment of an individual's ability to maintain a DHEAS set point, through examination of multiple DHEAS levels over time, may provide insight into biologic aging.

Methods. Using Cox proportional hazard models, we examined the relationship between DHEAS trajectory patterns and all-cause death in 950 individuals aged ≥ 65 years who were enrolled in the Cardiovascular Health Study and had DHEAS levels measured at three to six time points.

Results. Overall, there was a slight decline in DHEAS levels over time (-0.013 $\mu\text{g/mL/y}$). Three trajectory components were examined: slope, variability, and baseline DHEAS. When examined individually, a steep decline or extreme variability in DHEAS levels was associated with higher mortality ($p < .001$ for each), whereas baseline DHEAS level was not. In adjusted models including all three components, steep decline (hazard ratio [HR] 1.75, confidence interval [CI] 1.32–2.33) and extreme variability (HR 1.89, CI 1.47–2.43) remained significant predictors of mortality, whereas baseline DHEAS level remained uninformative of mortality (HR 0.97 per standard deviation, CI 0.88–1.07). The effect of trajectory pattern was more pronounced in men than in women. Individuals with both a steep decline and extreme variability in DHEAS levels had a significantly higher death rate than those with neither pattern (141 vs 48 deaths per 1,000 person-years, $p < .001$).

Conclusions. Our data show significant heterogeneity in the individual trajectories of DHEAS levels and suggest that these trajectories provide important biologic information about the rate of aging, whereas the DHEAS level itself does not.

Key Words: DHEA—DHEAS—Mortality—Aging—Elderly.

MAINTENANCE of homeostasis is a fundamental mechanism for survival. With increasing age, there is a decreased ability to handle threats to homeostasis, though the rate at which this happens at the individual level varies greatly (1). At present, there is no established way to measure one's ability to maintain homeostasis (2). Determination of hormonal status may provide insight because metabolic regulation is important to maintaining homeostasis.

Dehydroepiandrosterone sulfate (DHEAS) is the circulating sulfated conjugate of dehydroepiandrosterone (DHEA), a steroid synthesized mainly in the zona reticularis of the adrenal gland. This portion of the adrenal gland is large in fetal life and shrinks progressively with age after puberty. DHEA has no known direct hormonal activity in humans but may serve as a precursor for androgenic and estrogenic steroids. Circulating levels of DHEAS are lower in older than in younger people, resulting in mean levels at

age 65 that are less than a fifth of mean levels at age 20 (3,4). This finding has led to speculation that lower levels of DHEAS in older people contribute to the aging process and has driven widespread over-the-counter DHEA supplement use. However, DHEA replacement studies in older adults have failed to support the role for DHEAS as an antiaging hormone (5).

Furthermore, not all individuals experience a steady decline in DHEAS levels with age (6–9). Beyond the absolute DHEAS level, the way that a DHEAS level changes over time may provide insight into an individual and his/her ability to maintain homeostasis and thereby the way that they age. We sought to use analysis of trajectories of DHEAS to examine the biology of aging at the population level. We hypothesized that, irrespective of the actual level of DHEAS, older individuals with stability in DHEAS levels over time would have better survival than those with significant deviations, such as a steep decline or extreme variability. We also

hypothesized that there would be differences between men and women in the effects of these deviations because of sex-specific differences in the underlying hormonal milieu.

METHODS

Study Population

These analyses are based on data from the Cardiovascular Health Study (CHS) (10). The CHS is a population-based longitudinal study of risk factors for the development of cardiovascular disease (CVD) in 5,888 adults aged 65 years and older. Enrollment of an original cohort of 5,201 adults occurred between May 1989 and June 1990, and an additional cohort of 687 African Americans was enrolled in 1992–1993. Eligible individuals were identified from an age- and gender-stratified random sample of the Medicare eligibility rosters in four U.S. communities: Washington County, Maryland; Pittsburgh (Allegheny County), Pennsylvania; Sacramento County, California; and Forsyth County, North Carolina. To be eligible, individuals had to be noninstitutionalized, expecting to remain in the area for the following 3 years, not under active treatment for cancer, not wheelchair bound in the home, and not requiring a proxy respondent at entry. Household members of the sampled individual were recruited, if eligible. The institutional review boards of all four sites and the coordinating center at the University of Washington in Seattle approved the study. All participants gave informed consent.

At the initial visit, a detailed medical history, physical examination, and health status assessment were performed. Blood was drawn after a 12-hour fast and serum was frozen in -70°C freezers for future investigations. Participants in the original cohort subsequently returned annually for nine additional interviews and examinations. Those in the African American cohort underwent a comparable baseline examination and returned annually for six additional interviews and examinations. Fasting plasma specimens were collected at the 1989–1990, 1992–1993, 1993–1994, 1994–1995, 1996–1997, and 1997–1998 visits.

After exclusion of individuals taking corticosteroid preparations, estrogens, DHEA, or growth hormone at any phlebotomy time point, a random sample of 1,250 participants (500 men and 500 women from the original cohort and 125 men and 125 women from the new cohort) was selected for measurement of DHEAS levels. Sampling was otherwise performed without knowledge of baseline health status, blood availability, or subsequent survival.

DHEAS Analyses

DHEAS assays were performed at the Laboratory for Clinical Biochemistry Research (LCBR) at the University of Vermont in Burlington, Vermont. Plasma DHEAS levels were measured in duplicate by a competitive enzyme immunoassay kit (American Laboratory Products Company,

Salem, NH) from frozen specimens. All samples from a given participant were retrieved from storage and assayed in the same batch and all kits and reagents were purchased from the same lot to reduce interassay variability. The assay has a detection range 0.005–10 $\mu\text{g}/\text{mL}$ (0.01–27.1 $\mu\text{mol}/\text{L}$), and the interassay coefficient of variation (CV) range was determined in the LCBR to be 3.83%–7.19%. A previous study has shown the stability of DHEAS levels in samples stored for up to 15 years (3). Data from three studies show low within-subject variability in DHEAS levels in healthy subjects over time, supporting its use as an indicator of long-term DHEAS status (3,4,11).

Assessment of Covariates

Five comorbid conditions assessed at baseline were included as covariates: CVD, defined as a history of coronary heart disease, claudication, congestive heart failure, stroke, or transient ischemic attack; current lung disease, defined by self-report of physician diagnosis of emphysema, chronic bronchitis, or asthma; diabetes, defined by a fasting serum glucose of at least 126 mg/dL or the use of insulin or oral hypoglycemic medications; cancer in the past 5 years, defined by self-report of physician diagnosis; and depression, defined as a Center for Epidemiological Studies-Depression scale score of ≥ 8 on a modified 10-item scale (12).

Ascertainment of Events

Deaths were ascertained through the participant surveillance that has occurred every 6 months since the study inception. Confirmation of deaths was conducted through reviews of obituaries, medical records, death certificates, and the Health Care Financing Administration's health care utilization database for hospitalizations. Contacts and proxies were also interviewed for participants unavailable for follow-up. Ascertainment of mortality in the CHS is 100%. The incident events in this report occurred through June 30, 2006.

Statistical Analysis

Because a minimum of three measurements are required to define variability, we included data from 950 men and women who had plasma available at three to six time points (average five time points) over the first 8 years of CHS for analysis of trajectories. To assess the potential for selection bias, we compared the 950 individuals included in the current analysis with (a) the overall CHS cohort ($n = 5,888$) and (b) the men and women in our random sample with only one or two DHEAS measurements ($n = 300$). Compared with the full CHS cohort, our analytic sample was of slightly lower age but had similar baseline comorbid status. Consistent with the requirement of surviving long enough to have at least three blood measures collected, the mortality rate was lower in our analytic sample than in those with only one or two DHEAS levels obtained and than the full CHS cohort.

Table 1. Baseline Characteristics of Participants

Characteristics	Men (N = 466)	Women (N = 484)
Age, mean (SD), y	72.5 (5.1)	73.2 (5.7)
African American, n (%)	106 (23)	122 (25)
Cardiovascular disease, n (%)	144 (31)	98 (20)
Lung disease, n (%)	34 (7)	45 (9)
Diabetes, n (%)	89 (19)	72 (15)
Cancer, n (%)	32 (7)	20 (4)
Depression, n (%)	66 (14)	106 (22)
DHEAS, median (IQR), (µg/mL)	0.82 (0.51–1.20)	0.51 (0.33–0.76)

Note: DHEAS, dehydroepiandrosterone sulfate; IQR, interquartile range.

To allow interpretation on a relative scale, DHEAS levels were log transformed. We subsequently examined the distributions of baseline DHEAS level, trajectory slope, and variability around the trajectory. The slope on the log scale can be interpreted as the annual relative change in the original nontransformed scale. The variability around the trajectory was calculated by determining the standard deviation of the error in a model with a linear trajectory, which is equivalent to the CV in the original scale.

Cox proportional hazard models were performed to estimate the relative hazard of mortality. Slope and CV were modeled as time-varying covariates; at each DHEAS measure, slope and CV were recalculated using all measures through that date. By updating slope and CV at each DHEAS measurement, the hazard ratios (HRs) were estimated with respect to current, not future, exposure status. Subject-specific slope and CV were estimated in a single step. Robust standard errors and 95% confidence intervals (CIs) were estimated to account for repeated observations per participant. Because three DHEAS measures were required for inclusion, participants entered the analysis on the date of the third DHEAS measurement. Median time from entry for analysis was 10.9 years. Relative hazards of mortality by decile of baseline $\ln(\text{DHEAS})$ level, slope, and CV were estimated and plotted as decile plots. The decile plot was selected as a nonparametric way to determine the possible shape of the relationship of each trajectory parameter with mortality. Visual inspection was performed to examine for potential nonlinear effects, and, when found, threshold cutpoints were defined to determine risk categories. All models were adjusted for age, race, and sex and additionally adjusted for five comorbid conditions (CVD, pulmonary disease, diabetes, cancer, and depression) for both sexes combined and stratified by sex. Interactions of baseline DHEAS, slope, and CV with covariates were assessed using the likelihood ratio test. Apart from interactions with sex, no notable interactions were found. There was also no evidence of interaction by the number of DHEAS time points. The proportional hazards assumption was examined using a test based on Schoenfeld residuals.

RESULTS

At study entry, the mean age of men was 72.5 years and of women was 73.2 years (Table 1). The study sample was

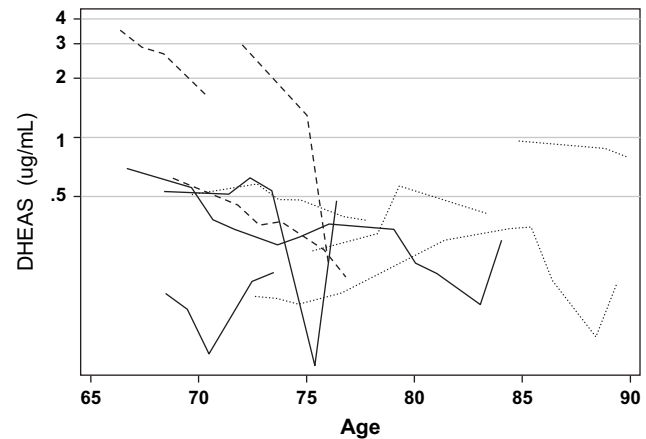


Figure 1. Sample of dehydroepiandrosterone sulfate (DHEAS) trajectory plots by age. Multiply by 2.714 to convert µg/mL to µmol/L.

24% African American and had a distribution of comorbidity in both sexes that would be expected in community-dwelling older adults. As expected, men had higher DHEAS levels, on average, than women did.

Overall, there was a slight decrease in DHEAS levels over time, at 0.013 µg/mL/y. However, there was significant heterogeneity in the pattern of DHEAS levels over time, as shown by a subsample of trajectory plots in Figure 1. We examined three different aspects of the trajectory in all subsequent analyses: the baseline DHEAS value, the trajectory slope, and the trajectory variability. There were 521 deaths over the course of follow-up. Inspection of plots of mortality risk by decile of each of the trajectory parameters revealed nonlinear associations for slope and variability, but not baseline DHEAS level (Figure 2). Rather than model these as linear associations, we determined thresholds for slope (Decile 1, steep decline; Deciles 2–10, no steep decline) and variability (Deciles 1–7, minimal variability; deciles 8–9, moderate variability; Decile 10, extreme variability).

Individuals with a steep decline in slope were more likely to die during follow-up than those without a steep decline in slope (Figure 3). Likewise, individuals with extreme variability had greater mortality than those with minimal variability. Individuals with both a steep decline and extreme variability in DHEAS levels had a significantly higher death rate than those with neither pattern (141 vs 48 deaths per 1,000 person-years, $p < .001$).

In adjusted models examining each trajectory component separately, individuals with a steep decline in DHEAS levels had higher mortality (hazard ratio [HR] 1.99, 95% CI 1.50–2.64) than those with no decline (Table 2). Individuals with extreme (HR 2.09, 95% CI 1.63–2.67) or moderate (HR 1.36, 95% CI 1.11–1.67) variability in DHEAS levels over time had a higher mortality than those with minimal variability, whereas baseline DHEAS level was not associated with mortality (HR 0.95 per standard deviation, 95% CI

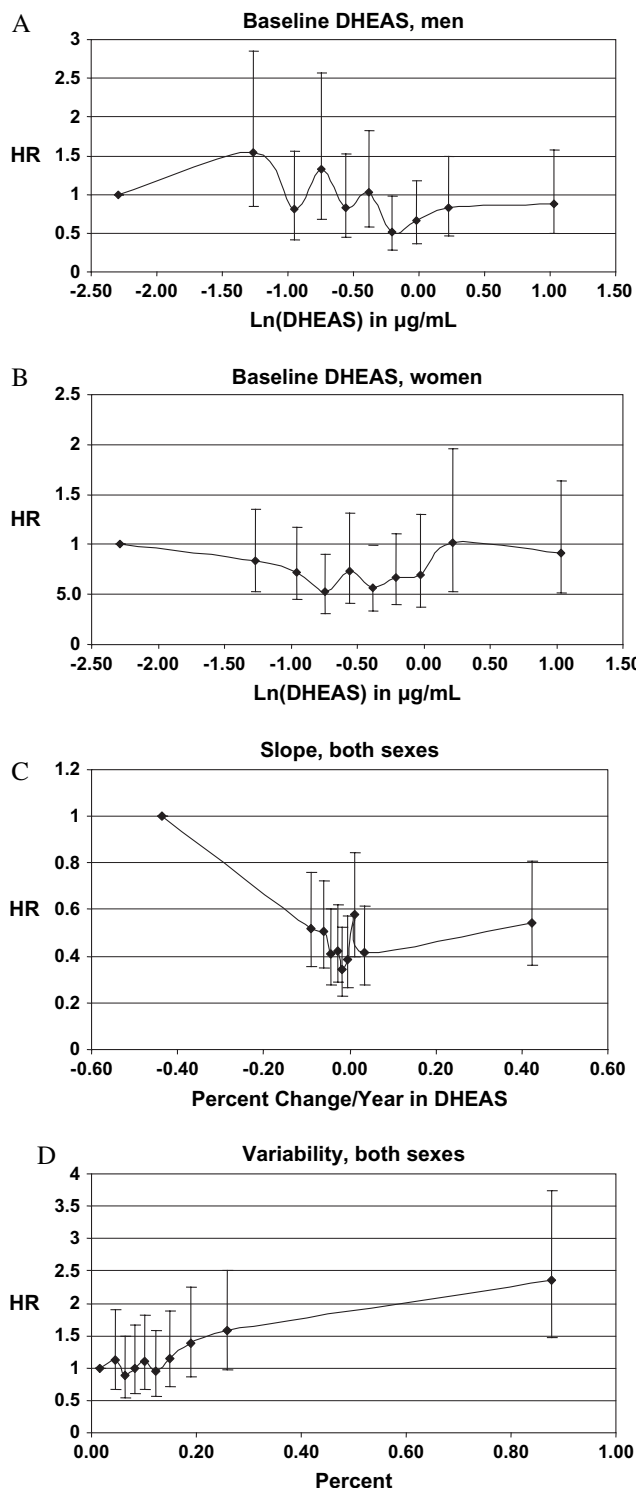


Figure 2. Hazard ratio of mortality by decile of each dehydroepiandrosterone sulfate (DHEAS) trajectory parameter. (A) Baseline (men), (B) baseline (women), (C) slope, and (D) variability. Each point represents the median value of a decile. Decile 1 is the reference category in each plot. Vertical bars show 95% confidence limits. Models were adjusted for age, race, and sex. HR, hazard ratio.

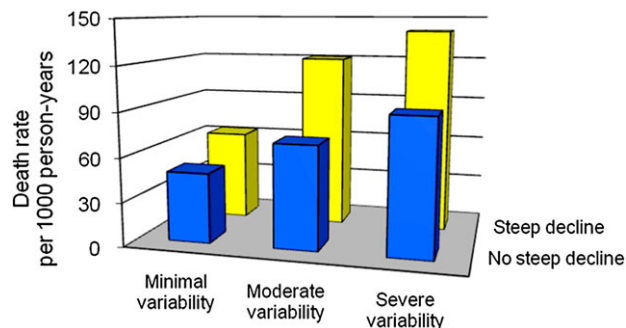


Figure 3. Death rate by dehydroepiandrosterone sulfate (DHEAS) slope and variability category.

0.86–1.04). In models including all three components, steep decline (HR 1.75, 95% CI 1.32–2.33), moderate variability (HR 1.29, 95% CI 1.05–1.59), and extreme variability (HR 1.89; 95% CI 1.47–2.43) remained significant predictors of mortality, whereas baseline DHEAS level remained un-predictive of mortality (HR 0.97, 95% CI 0.88–1.07). Additional adjustment for caloric intake and physical activity did not significantly affect these estimates.

Despite similarity in threshold cutpoints between men and women on the decile plots, the relationship between the trajectory pattern and mortality was stronger in men than in women (Table 2). The interaction terms with sex were statistically significant for DHEAS slope ($p = .04$) and CV ($p = .0006$) categories, but not for baseline DHEAS level ($p = .40$). In models including all three components, steep decline (HR 2.08, 95% CI 1.46–2.98) and extreme variability (HR 2.91, 95% CI 2.07–4.11) were highly associated with mortality in men, whereas only moderate variability (HR 1.47, 95% CI 1.09–1.97) was statistically significantly related in women. In these models, baseline DHEAS level remained unrelated to mortality in both sexes. The baseline DHEAS level was modeled in women to allow for a potential U-shaped relationship evident in the sex-stratified decile plots and previously shown in a cohort of disabled women (13), though even with this modeling strategy, the association between baseline DHEAS and mortality did not achieve statistical significance in the final model.

DISCUSSION

We report independent associations of steep decline and extreme variability in DHEAS levels with mortality, whereas the absolute DHEAS level was not associated with mortality in a population-based cohort of men and women aged 65 years or older. This finding suggests that the absolute level of DHEAS, which is highly genetically influenced (14,15), is less clinically relevant than an individual’s ability to maintain that set point. Furthermore, it provides evidence to support the premise that the optimal way to age is both slowly (no or slow rate of decline) and uniformly (small standard deviation in the rate of decline) (16).

Table 2. Mortality Risk by DHEAS Trajectory Parameter*

Model	Measure	Both sexes	Men only	Women only	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	
Baseline [†] only	Baseline	0.95 (0.86–1.04)	0.93 (0.81–1.07)	1.37 (1.03, 1.83)	
				1 1.41 (0.95–2.09)	
Slope [‡] only	No steep decline	1	1	1	
	Steep decline	1.99 (1.50–2.64)	2.53 (1.74–3.67)	1.51 (0.98–2.33)	
Variability [§] only	Minimal variability	1	1	1	
	Moderate variability	1.36 (1.11–1.67)	1.24 (0.93–1.64)	1.51 (1.13–2.03)	
	Extreme variability	2.09 (1.63–2.67)	3.33 (2.37–4.67)	1.38 (0.95–1.98)	
Baseline [†] , slope [‡] , and variability [§]	Baseline	0.97 (0.88–1.07)	0.99 (0.86–1.13)	1.33 (0.99–1.78)	
				1 1.34 (0.90–2.00)	
		No steep decline	1	1	1
		Steep decline	1.75 (1.32–2.33)	2.08 (1.46–2.98)	1.34 (0.86–2.10)
		Minimal variability	1	1	1
		Moderate variability	1.29 (1.05–1.59)	1.13 (0.84–1.52)	1.47 (1.09–1.97)
		Extreme variability	1.89 (1.47–2.43)	2.91 (2.07–4.11)	1.27 (0.87–1.85)

Notes: CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; HR, hazard ratio.

*All models adjusted for age, race, cardiovascular disease, pulmonary disease, diabetes, cancer, and depression. Models of combined sexes were also adjusted for sex.

[†]Baseline DHEAS level reported per standard deviation for both sexes and men only, categorized into three categories (Decile 1–2, Decile 3–8 [reference], and Decile 9–10) for women only.

[‡]The cutpoint separating not steep and steep decline is $-0.11\%/y$.

[§]The cutpoints separating minimal, moderate, and extreme variability are 0.17% and 0.30%.

Our study confirms the previous cross-sectional and longitudinal data showing an overall decline in DHEAS levels with increasing age and shows a similar magnitude of decline (3,4,6–9). However, our data demonstrate considerable heterogeneity among individuals in rates of change of DHEAS and, in a subset, substantial instability over time. This has implications for DHEA supplementation because our data suggest that there are significant endogenous fluctuations in DHEAS levels. It is also of particular concern because DHEA has not been subjected to the same rigor of clinical testing as other hormonal preparations due to its status as an over-the-counter supplement. The largest clinical trials in older people, the longest of which was 2 years in duration, do not support health benefits to DHEA supplementation (17–19). The long-term health risks or benefits of DHEA supplementation are unknown and particularly not on a background of varying endogenous levels.

Studies in humans, rather than in animal models, are required to understand the physiological roles of DHEAS because DHEAS is not produced in mice or rats but only in higher order primates and humans (20). Observational studies conducted in older populations have generally reported lower mortality in men with higher DHEAS levels and no association or a U-shaped relationship in women (13,21), whereas we found no association of the absolute level of DHEAS with mortality in either sex. Roth and coworkers (22) have shown that calorically restricted monkeys have higher DHEAS levels and live longer than monkeys on an unrestricted diet, supporting a role for DHEAS as a potential biomarker of aging. However, DHEAS levels were not

affected by a 6-month study of caloric restriction in younger people (23).

Although the adverse DHEAS trajectory patterns precede mortality, we cannot determine whether the changes in DHEAS levels contribute to mortality or are markers of the underlying health status of the individual. DHEAS may have biologic importance as a precursor to estrogens and androgens and as neurotransmitter in the brain (24). Nevertheless, we favor the interpretation that the DHEAS trajectory reflects the underlying health status of the individual. Steep decline or extreme variability in other health parameters, such as blood pressure (25), has also been associated with an increase in mortality rate. To our knowledge, this type of trajectory analysis has not been previously extended to examination of a putative biomarker of aging.

We also cannot determine whether the physiological genesis of steep decline and extreme variability in DHEAS levels is the same. Large variability in DHEAS levels suggests a complete inability of the individual to make adjustments to cope with internal changes and external stressors. Whereas minor changes in DHEAS levels could represent appropriate restoration of equilibrium, constantly fluctuating DHEAS levels are likely to be measuring a lack of adaptive capacity characteristic of frailty (26).

The sex difference in the strength of association between trajectory pattern and mortality is intriguing. If DHEAS played a causal role, it would be expected to be more influential in women than in men. This is due to lower levels of endogenous androgens and estrogens and increased conversion of DHEAS to DHEA in postmenopausal women (27,28), which should result in a decreased ability to buffer

changes in DHEAS level. Fried and associates (29) have previously reported a mortality difference between men and women enrolled in CHS. Adjustment for a large battery of traditionally measured predictors of mortality significantly diminished the association between age and mortality, demonstrating that these factors explained much of the effect of age, but they did not attenuate the twofold higher mortality of men compared with women. These findings suggest that there must be other factors, not traditionally measured in epidemiological studies of older people, which contribute to the greater longevity of women. Our data suggest a relative impairment of homeostasis and increased susceptibility in these older men, or a physiological resilience in women, in the face of the factors that lead to adverse DHEAS trajectory patterns.

A major strength of our study is the use of a large, multi-center, population-based cohort comprised older men and women who had serial examinations and phlebotomy, with up to 17 years of follow-up. However, our results may not be generalizable to younger populations, as we have no data on individuals who are younger than 65 years. Also, because we are using observational data, we cannot determine whether the hormonal trajectory is a sensitive marker of physiological dysregulation or whether alterations in the dynamics of DHEAS mediate physiological effects. Our data support thresholds of slope and variability in relation to mortality, and therefore, the DHEAS measures were modeled using cutpoints. However, the specific threshold values identified in this investigation represent estimates from our data and should be confirmed in other cohorts.

In summary, our data suggest that trajectories of DHEAS provide more biologic information about an older individual than the DHEAS level itself. This research is a departure from disease-based models of aging and instead focuses on age-related physiological susceptibility and resilience, which currently lack objective measures. In fact, the point estimates of mortality risk for steep decline and extreme variability were larger than those of any of the five baseline diseases we included as covariates, suggesting that the trajectory parameters were stronger predictors of mortality than established predictors such as CVD or diabetes mellitus. Although we are the first, to our knowledge, to examine the relationship between the pattern of a hormonal measure, irrespective of its absolute level, and mortality, it is likely that the dysregulation in DHEAS levels is also paralleled in other physiological systems. Trajectory analysis provides the opportunity to study the biology of aging at the population level and potentially offers insight into the dynamic process of maintaining homeostasis.

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CORRESPONDENCE

Address correspondence to Dr. Anne R. Cappola, MD, ScM, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Pennsylvania School of Medicine, 764 CRB, 415 Curie Boulevard, Philadelphia, PA 19104. Email: acappola@mail.med.upenn.edu

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