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Cortisol, dehydroepiandrosterone sulphate, their ratio and all-cause and cause-specific mortality in the Vietnam Experience Study

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Abstract

Objectives: The aim of these analyses was to examine the association between cortisol, dehydroepiandrosterone sulphate (DHEAS), and the cortisol:DHEAS ratio and mortality.

Design: This was a prospective cohort analysis. **Methods:** Participants were 4255 Vietnam era US army veterans. From military service files, telephone interviews, and a medical examination, occupational, socio-demographic, and health data were collected. Contemporary morning fasted cortisol and DHEAS concentrations were determined. Mortality was tracked over the subsequent 15 years. The outcomes were all-cause, cardiovascular disease, cancer, other medical mortality and external causes of death. Cox proportional hazard models were tested, first with adjustment for age and then additionally adjusting for a range of candidate confounders. **Results:** In general, cortisol concentrations did not show an association with all-cause or cause-specific mortality. However, in age- and fully-adjusted analyses, DHEAS was negatively related to all-cause, all cancers, and other medical mortality; high DHEAS concentrations were protective. The cortisol:DHEAS ratio was also associated with these outcomes in both age- and fully-adjusted models; the higher the ratio the greater the risk of death. **Conclusions:** DHEAS was negatively, and the ratio of cortisol to DHEAS was positively associated with all-cause, cancer, and other medical cause mortality. Further experimental study is needed to elucidate the mechanisms involved in these relationships.

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The corticosteroid hormone cortisol, a component of the hypothalamic-pituitary-adrenal (HPA) axis, has a key role in the stress response [1], and has some immunosuppressive effects [2]. Higher circulating cortisol levels have been observed in critically ill intensive care patients [3], such as those experiencing septic shock and trauma [4]. Another adrenal cortex hormone, dehydroepiandrosterone (DHEA), is a precursor to sex hormones and is present in the circulation, predominantly as its sulphated form dehydroepiandrosterone sulphate (DHEAS). DHEA/DHEAS appears to counterbalance many of the negative effects of cortisol on immunity [5, 6]. For example, it has been shown *in vitro* that higher cortisol suppresses neutrophil function and this effect can be overcome by co-incubation with DHEAS [7, 8]. Higher levels of DHEAS are also associated with less serious illness among intensive care patients [3, 4, 9]. Moreover, it appears that the activity of the HPA axis as reflected in the ratio of cortisol to DHEA is particularly important with regard to health. The production of DHEAS declines in older age, a phenomenon termed adrenopause, while the production of cortisol remains stable, resulting in higher cortisol:DHEA ratios. This altered ratio has been associated with the age-related loss of immunity (immunesenescence), [2, 7, 10] as well as with non-immunity related psychological outcomes such as higher anxiety, mood disturbance, confusion, and poorer cognitive performance [11].

In cohort studies, cortisol and DHEA levels have also been linked to mortality. For example, higher cortisol was associated with increased mortality in patients with heart failure[12], sepsis [13], and stroke [14], although this is not a universal finding [15]. DHEAS has been shown to be negatively associated with total and cardiovascular disease mortality in selected studies. in women with ischaemic heart disease [16], all-cause mortality in men only[17, 18], both sexes [19] and both all-cause

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and cardiovascular disease mortality in older people [20]. Others have found no association with either disease or all-cause mortality [21]. Surprisingly, few studies have examined the cortisol:DHEA/S ratio in association with mortality. However, one study of septic shock and trauma patients revealed higher cortisol, lower DHEAS, and a higher cortisol:DHEA ratio among those who were more seriously ill and non-survivors [4]. The ratio also predicted all-cause but not disease mortality in US men who had fought in Vietnam in the present sample [22]. What is not known is whether serum cortisol and DHEAS alone predict all-cause mortality in this sample, and whether cortisol, DHEAS, and their ratio are associated with mortality from other causes such as cancer and non-medical causes. As cortisol, DHEAS, and their ratio are associated with a variety of health outcomes, particularly immune-related measures [7, 10, 23, 24]), it might be expected that they relate to death from particular causes. Consequently, the present analyses examined the association between cortisol, DHEAS, their ratio and all-cause, cardiovascular disease, cancer mortality, other medical causes, and external causes of death in a substantial cohort of male military veterans.

Materials and Methods

Sample

Participants (N = 4255) were identified retrospectively from data gathered as part of the Vietnam Experience Study; an epidemiological study commissioned by the US congress to investigate the health consequences of the military experiences of Vietnam veterans. Participants were male military personnel drawn from approximately five million US Vietnam-era Army veterans whose service files were stored at the National Personnel Records Center [25]. The Centers for Disease

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Control, Atlanta, had access to U.S. Veteran Administration records and provided the authors with a fully anonymised dataset. Ethical approval for the study was given by the various relevant bodies, including the US Centers for Disease Control. Eligibility criteria are published elsewhere, and the final cohort with complete data included 18,313 former military personnel [25-27].

Data collection

Information pertaining to place of service and ethnicity was extracted from the military archives. Participants were designated as being Vietnam veterans if they had served at least one tour of duty in Vietnam, and as non-Vietnam veterans if they did not (this group included men who served one or more tours of duty in Korea, Germany or the US). The ethnic origin of the study members were classified as 'white', 'black', or 'other'; the latter group comprising Hispanics, Asians, Pacific Islanders, American Indians, and Alaskan Natives. Of those included in the original cohort, 17,867 were considered to be alive on December 31, 1983 and therefore eligible for active follow-up. In 1985, participants were invited to participate in a telephone interview. Of those traced (N = 16,349), 15,288 men were able to participate in the 1985 telephone survey (85.6% of those alive on December 31st 1983) [27]. From the telephone survey, educational grade achieved at school ($\leq 11^{th}$ grade, 12^{th} grade, $>12^{th}$ grade) and household income in midlife ($\leq$ \$20k; -\$40k, > \$40k per year) were determined as measures of socio-economic status. Frequency of alcohol consumption (units per week), cigarette smoking habits and marital status were ascertained using standard questions. Participants were also asked whether or not they had a range of somatic physician-diagnosed health problems which included hypertension, cancer, diabetes and coronary heart disease [28, 29].

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In 1986, a random sample of telephone interview respondents (N=6,443) were invited to attend a three day medical examination with orientation at a single facility in Albuquerque, New Mexico, for which travel expenses and a nominal stipend were paid; 4,462 men representative of the original cohort attended (69.3% of those invited). The mean age at medical examination was 38.3 years (range: 31.1 to 49.0). The final number of participants with complete data after the medical examination was 4,256. This group represents 23.3% of persons originally enrolled in the study. Serum cortisol and DHEAS were assayed in serum from a fasted blood sample using a double antibody radioimmunoassay system (Leeco Diagnostics, Inc., Southfield, MI). All laboratory assays were assured by using bench and blind repeat controls. The blind repeat tests were run for one in 20 randomly chosen samples; the correlations between first and repeat samples exceeded 0.98. Bench controls yielded intra and inter-assay coefficients of variation that were all < 10%. With the participant in a sitting position, a registered nurse, using a standard mercury sphygmomanometer measured blood pressure twice consecutively, from both arms. For analysis, an average of the two right arm systolic and diastolic blood pressure values was computed. Measurements from the left arm were used to verify individual results.

The vital status of men between army discharge and December 31st 1983 (the date the cohort was established) was ascertained by cross-checking against a variety of mortality databases supplied by the US army, the Veterans Administration (Beneficiary Identification and Records Locator Subsystem), the Social Security Administration, the Internal Revenue Service, and the National Center for Health Statistics (National Death Index). Vital status post-medical exam continued to be

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ascertained until 31st December 2000 using the mortality databases described above. Mortality due to major CVD was classified using the International Classification of Diseases (ICD) [30] codes: ICD-9: 390–434,436–448, and ICD-10: I00–I78 which comprised: acute rheumatic fever; chronic rheumatic heart diseases; hypertensive diseases; ischaemic heart diseases; pulmonary heart disease and diseases of pulmonary circulation; other forms of heart disease; cerebrovascular diseases; diseases of arteries, arterioles and capillaries. The CVD mortality variable thus encompasses death from a variety of disorders; the bulk of the deaths were from ischaemic heart diseases. Mortality from cancer was classified using the International Classification of Diseases (ICD) codes: ICD-9: 140–239, ICD-10: C00–D48 which include malignant neoplasms of all specified areas, Hodgkins disease, non-Hodgkins lymphoma, leukaemia, multiple myeloma, immunoproliferative neoplasms, and other malignant neoplasms of unspecified areas. Of the cancers, the most frequent cause of death (N = 19) was from malignant neoplasms of the trachea, bronchus and lung. External causes of death included those coded as ICD-9: E800–E999, ICD-10: V01–Y8, including accidents, suicide, and homicide. Half of the deaths in this category were from suicide or homicide. Finally, 'other' causes of death were calculated as all-cause mortality minus the other classifications, and consisted of infectious diseases, liver diseases/failure, kidney diseases/failure, and respiratory diseases. The most frequent causes of death in this category were from infection, including infection with Human Immunodeficiency Virus (HIV), and from liver disease. 4255 men were included in the analyses reported below.

Statistical analysis

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Due to their skewed distribution, cortisol and DHEAS values were log–transformed, as was the cortisol:DHEAS ratio. All covariates analysed in the study conformed to the assumption of proportional hazards over time; partial residuals were all randomly distributed. Having confirmed that the proportional hazards assumption had not been violated, Cox' proportional hazard regression was used to examine the relationships between cortisol, DHEAS, their ratio and mortality, in age-adjusted analyses. Demographic, military service, health behaviour and metabolic variables were compared between those who had and had not died using univariate Cox' proportional hazard regression. Further multivariate analyses of the relationships between cortisol, DHEAS, their ratio and mortality were then run, additionally adjusting for significant covariates, including some or all of place of service, ethnicity, marital status, alcohol consumption, smoking, household income, and physical illness diagnosis. Only those covariates significant in the univariate prediction of mortality were included as covariates in the fully-adjusted models.

Results

All-cause mortality

The arithmetic mean (SD) serum cortisol and DHEAS values for the whole sample were 18.2 (5.52) and 239.8 (99.86) µg/dl, respectively. This equates to 502.1 (152.30) and 832.1 (346.51) nmol/L, respectively. The mean (SD) cortisol to DHEAS ratio was 0.09 (0.06). During the 15 years of follow-up there were 236 deaths. Table 1 shows the univariate predictions of all-cause mortality. Higher mortality was associated with service in Vietnam rather than another overseas location, not being married, being non-white, smoking, having a physical illness, lower household income in midlife, higher systolic blood pressure (SBP), and higher alcohol consumption. Table 1 also shows

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the univariate hazard ratios for cortisol, DHEAS, and cortisol:DHEAS ratio predicting all-cause mortality. Age-adjusted analyses revealed that higher cortisol concentrations were associated with a higher all-cause mortality risk, hazard ratio (HR) = 1.71, 95% confidence interval (CI) = 1.12 – 2.62, p = .013. Conversely, those with higher DHEAS levels were at a decreased risk of death, HR = 0.51, 95%CI = 0.38 – 0.66, p < .001. The cortisol:DHEAS ratio was significantly related to mortality risk, HR = 2.05, 95%CI = 1.61 – 2.61, p < .001, such that individuals with a higher ratio were at greater risk of death. Following adjustment for age and the other covariates collectively, the association between cortisol and mortality was no longer statistically significant at conventional levels (HR = 1.32, 95%CI = 0.86 – 2.03, p = .20). However, higher DHEAS levels were still related to lower mortality risk, HR = 0.55, 95%CI = 0.43 – 0.71, p < .001, and the cortisol:DHEAS ratio remained significantly and positively associated with mortality, HR = 1.76, 95% CI = 1.40 – 2.23, p < .001.

[Insert Table 1 about here]

Cardiovascular disease and cancer mortality

Sixty-three participants died of CVD; Table 2 shows the hazard ratios for the univariate predictors of CVD mortality. Participants who had died of CVD were slightly older, were more likely to have served in Vietnam than another overseas location, were more likely to be divorced/widowed/separated, Black, smokers, in the lowest household income in midlife tertile, and have a physical illness, higher systolic blood pressure (SBP), but not have higher alcohol consumption. Table 2 also presents the univariate hazard ratios for cortisol, DHEAS, and their ratio

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predicting CVD mortality status. Age adjusted analyses indicated that cortisol, DHEAS, and the cortisol:DHEAS ratio were not associated with CVD mortality. The hazard ratios for the univariate predictors of mortality from cancer are also presented in Table 2. Of the covariates tested only age, presence of physical illness, and smoking were significantly associated with death from cancer. There was no significant association between cortisol and cancer mortality. However, in age adjusted models, higher DHEAS concentrations were associated with a reduced risk of death from cancer, HR = 0.40, 95%CI = 0.22 – 0.71, p = .002, and a higher cortisol:DHEAS ratio was associated with an increased cancer mortality risk, HR = 1.94, 95%CI = 1.13 – 3.34, p = .02. In the fully adjusted models, higher DHEAS concentrations were still related to lower mortality risk, HR = 0.40, 95%CI = 0.23 – 0.70, p = .001, and a higher cortisol:DHEAS ratio still associated with an increased risk of death from cancer, HR = 2.04, 95%CI = 1.19 – 3.48, p = .01.

[Insert Table 2 about here]

Non medical and other causes of death

The univariate hazard ratios predicting death from non medical causes are presented in Table 3. Those who died from non medical causes had smaller household incomes in mid life. In age adjusted models, cortisol, DHEAS, and their ratio were not associated with non-medical causes of death. The univariate predictions of mortality from other causes are also summarised in Table 3. Those who died from other causes were more likely to be smokers, consumed more alcohol, had higher blood pressure, were less likely to be white, had a lower household income in mid life, were less likely to be married and more likely to have a diagnosed chronic illness. In the age and fully

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adjusted models, cortisol was not associated with other causes of death, but DHEAS was again protective, HR = 0.33, 95%CI 0.21 – 0.51, $p < .001$, and HR = 0.45, 95%CI 0.30 – 0.67, $p < .001$, respectively. A higher cortisol:DHEAS ratio was related to an increased risk of death by other causes in age adjusted, HR = 3.11, 95%CI 2.07 – 4.66, $p < .001$, and fully adjusted models, HR = 2.11, 95%CI 1.46 – 3.06, $p < .001$. In the fully adjusted models, the other predictors of death from other causes were smoking, high alcohol consumption, high resting SBP, not being married, not being white, low income in midlife, and pre-existing physical illness.

[Insert Table 3 about here]

Discussion

In a population of male Vietnam era war veterans, age- and fully-adjusted analyses showed that DHEAS was associated with a reduced risk of all-cause, cancer, and other cause mortality. A higher cortisol:DHEAS ratio was associated with an increased risk of death from all causes, cancer, and other causes. DHEAS and the cortisol:DHEAS ratio were not associated with death from cardiovascular disease or non-medical causes. For the most part, cortisol concentrations did not predict mortality. Although there was a positive association between cortisol and all-cause mortality in the analysis that adjusted only for age, this was attenuated to non-significance in the fully adjusted model.

These findings are concordant with those of previous studies where DHEAS has been shown to be protective against all-cause mortality in a variety of populations [17-20]. Although negative

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associations between DHEAS concentrations and cardiovascular disease mortality have been reported [20, 31], which was not evident in the present sample, it is possible that this was a result of the older age (64 years+) of the participants in the previous studies, who would have naturally decreased DHEAS levels associated with ageing [32]. Only one study has demonstrated an association between DHEAS and cardiovascular mortality in men aged 30-80 years old [33]. In others, the association between DHEAS levels and cardiovascular disease mortality was lost after adjustment for a range of CVD risk factors[34]. Of the few studies examining the cortisol:DHEAS ratio and total mortality, our findings confirm previous links [4]. The failure of cortisol alone to predict mortality contrasts with some previous findings [12-14], but is in agreement with others [9, 15]. As we state above, DHEAS decreases with age [32], thus increasing the relative levels of cortisol, so it is possible that cortisol influences mortality in older as opposed to middle aged populations.

The extension to the literature that the present study provides is the evidence of associations with cancer and other cause mortality for both DHEAS and the cortisol:DHEAS ratio. These findings are not surprising given that the majority of other medical causes of death were largely infectious and immune (e.g. HIV) diseases, and that both cortisol and DHEA/DHEAS have been proposed to have a role in regulating immune function [5, 10, 23, 24]; DHEA/DHEAS is also considered protective against the immunosuppressive actions of cortisol [7]. There is also evidence that treatment with DHEA can enhance immune function in humans with low DHEA/DHEAS levels [35], and increase immune function in animals [36, 37], although the benefits of DHEA supplementation on immunity in general remain controversial [6, 38, 39]. Taken together, the data suggest that DHEA might contribute to mortality via immune function effects. Although we grouped malignancy sub-types that do not

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have a unifying aetiology into a single category, in general cancer is similarly an immune-regulated disease (see e.g., [40]), and links are evident between an altered HPA axis and inflammation in cancer patients [41]. It has also been suggested that low DHEA/S levels are associated with the initiation of cancer [42], suggesting a possible pathway by which lower DHEA/S concentrations and a higher cortisol:DHEA/S ratio could relate to cancer mortality.

It is perhaps not surprising that externally caused mortality was not significantly related to cortisol, DHEAS, or the cortisol:DHEAS ratio in this sample, given that it is difficult to conceive of mechanisms by which altered levels of such hormones would increase the likelihood of death from suicide, homicide, or accidents.

It is possible that the stress of army service could also contribute to neuroendocrine changes which in turn contribute to future morbidity and to the exacerbation of current disease, resulting in earlier mortality in this particular population. Others have suggested that inadequate adrenal functioning may be related to both psychological reactions to exposure to the stress of war and the biologic vulnerability to disease [43]. Indeed, chronic stress has been associated with alterations in HPA axis function [44] and changes in leukocyte trafficking and function (Chrousos, 1995). However, the mechanisms by which such stress-induced changes might relate to premature mortality are likely to be complex and diverse.

The present study has a number of limitations. First, in observational studies it is not possible to determine causality. It is possible that lower DHEAS and a high cortisol:DHEAS ratio may be

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markers for some or several unmeasured factors related to mortality, rather than a cause *per se*. For example, a high cortisol:DHEAS ratio might result from extant disease. Low DHEA secretion, for example, is frequently observed in patients with an adrenal cortisol-producing adenoma. However, the present findings for DHEAS and the cortisol:DHEAS ratio survived adjustment for a pre-existing diagnosis of cancer, diabetes and heart disease, and the circulating cortisol levels measured in this cohort are not unusually elevated, nor DHEAS unusually attenuated. Nevertheless, experimental studies would be necessary to establish a causal relationship. Second, the sample was exclusively male so these findings cannot be readily generalised to women. However, given that premenopausal women have lower circulating DHEAS [45], it is possible that the relationship between cortisol:DHEAS ratio and mortality in women might be even stronger. Third, this study only used a single morning measurement of serum cortisol and DHEAS. Cortisol has a diurnal rhythm which would be best captured through multiple measurements. However, the timing of the present samples was for the most part invariant across participants. Further, DHEAS concentrations remain stable throughout the day and reflect the 24-hour secretion of DHEA [46, 47].

In conclusion, in a sample of male Vietnam era war veterans, lower DHEAS and a higher cortisol:DHEAS ratio were associated with an increased risk of all-cause, cancer, and other cause mortality. Further, experimental studies would be necessary to elucidate mechanisms further and establish causality. It would be particularly instructive to examine the effects of DHEA supplementation in individuals with lower DHEA/S levels and/or high cortisol:DHEA/S ratios on mortality.

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Table 1: Univariate hazard ratios (95% confidence intervals) predicting all-cause mortality.

		All-cause mortality (N = 236)	
		HR (95% CI)	*p*
Age at medical examination (years)		1.04 (0.99 – 1.09)	.13
Units of alcohol per week		1.01 (1.01 – 1.02)	< .001
Systolic Blood Pressure (mmHg)		1.02 (1.01 – 1.03)	.001
Cortisol (µg/dL) logged		1.72 (1.13 – 2.64)	.01
DHEAS (µg/dL) logged		0.50 (0.38 – 0.65)	<.001
Cortisol : DHEAS logged		2.07 (1.63 – 2.64)	<.001
Place of service	Other overseas	0.71 (0.51 – 0.98)	.04
	US only	0.76 (0.53 – 1.08)	.12
	Ever in Vietnam	referent	-
Ethnicity:	Black	2.28 (1.67 – 3.13)	<.001
	Other	1.88(1.22 – 2.92)	.004
	White	referent	-
Household income in midlife	<$20,000	4.18 (2.62 – 6.66)	<.001
	-$40,000	2.20 (1.38 – 3.51)	.001
	>$40,000	referent	referent
Smoking Status:	Current smoker	2.01 (1.43 – 2.83)	< .001
	Ex smoker	0.94 (0.62 – 1.44)	.78
	Non smoker	referent	referent
Marital Status:	Never married	2.53 (1.75 – 3.66)	< .001
	Divorced/separated/widowed	2.32 (1.73 – 3.10)	< .001
	Married	referent	referent
Physical Illness	Yes	2.38 (1.78 – 3.18)	< .001
diabetes/hypertension/cancer or CHD	No	referent	referent

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Table 2: Univariate hazard ratios (95% confidence intervals) predicting mortality from CVD and cancer

		Died: CVD (N = 63)		Died: Cancer (N =47)	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age at medical examination (years)		1.13 (1.02 – 1.24)	.02	1.15 (1.03 – 1.29)	.01
Units of alcohol per week		1.01 (0.99 – 1.02)	.29	1.01 (0.99 – 1.02)	.26
SBP (mmHg)		1.03 (1.02 – 1.05)	<.001	1.02 (0.99 – 1.04)	.10
Cortisol (µg/dL) logged		2.21 (0.96 – 5.06)	.06	0.86 (0.34 – 2.18)	.74
DHEAS (µg/dL) logged		0.77 (0.44 – 1.35)	.36	0.37 (0.21 – 0.64)	<.001
Cortisol : DHEAS		1.62 (1.00 – 2.62)	.05	2.15 (1.26 – 3.66)	.005
Place of service	Other overseas	0.46 (0.22 – 0.95)	.04	1.08 (0.55 – 2.09)	.82
	US only	0.82 (0.43 – 1.56)	.54	0.88 (0.40 – 1.95)	.76
	Ever in Vietnam	referent	referent	referent	referent
Ethnicity	Black	1.98 (1.05 – 3.76)	.04	1.12 (0.47 – 2.64)	.80
	Other	2.11 (0.95 – 4.69)	.07	0.68 (0.17 – 2.83)	.60
	White	referent	referent	referent	referent
Household income in midlife	<$20,000	3.74 (1.55 – 9.03)	.003	1.37 (0.54 – 3.48)	.51
	-$40,000	2.12 (0.88 – 5.12)	.09	1.76 (0.77 – 4.02)	.18
	>$40,000	referent	referent	referent	referent
Smoking Status:	Current smoker	2.14 (1.07 – 4.30)	.03	3.49 (1.35 – 8.99)	.009
	Ex smoker	1.35 (0.61 – 3.00)	.47	1.97 (0.69 – 5.67)	.21
	Non smoker	referent	referent	referent	referent
Marital Status:	Never married	1.40 (0.59 – 3.30)	.44	0.54 (0.13 – 2.23)	.42
	Divorced/separated/widowed	1.95 (1.12 – 3.41)	.02	1.36 (0.69 – 2.69)	.37
	Married	referent	referent	referent	referent
Physical Illness	Yes	3.60 (2.14 – 6.04)	<.001	2.05 (1.04 – 4.02)	.04
diabetes/hypertension/cancer or CHD	No	referent	referent	referent	referent

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Table 3: Univariate hazard ratios (95% confidence intervals) predicting mortality from external and other causes of death

		Died: External (N = 63)		Died: Other (N =47)	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age at medical examination (years)		0.93 (0.83 – 1.04)	.20	0.98 (0.89 – 1.07)	.64
Units of alcohol per week		1.01 (0.99 – 1.02)	.19	1.02 (1.01 – 1.02)	<.001
SBP (mmHg)		0.98 (0.96 – 1.01)	.14	1.02 (1.00 – 1.04)	.02
Cortisol (µg/dL) logged		1.86 (0.74 – 4.66)	.18	2.08 (0.98 – 4.45)	.06
DHEAS (µg/dL) logged		0.76 (0.40 – 1.41)	.38	0.34 (0.22 – 0.53)	<.001
Cortisol : DHEAS		1.54 (0.90 – 2.63)	.11	2.95 (1.98 – 4.40)	<.001
Place of service	Other overseas	0.57 (0.27 – 1.18)	.13	0.84 (0.49 – 1.46)	.54
	US only	0.68 (0.31 – 1.46)	.32	0.69 (0.36 – 1.32)	.26
	Ever in Vietnam	referent	referent	referent	referent
Ethnicity	Black	1.08 (0.46 – 2.55)	.86	5.03 (3.08 – 8.21)	<.001
	Other	1.65 (0.65 – 4.18)	.29	3.07 (1.49 – 6.33)	.002
	White	referent	referent	referent	referent
Household income in midlife	<$20,000	4.57 (1.60 – 13.20)	.005	9.35 (3.37 – 25.94)	<.001
	-$40,000	2.63 (0.91 – 7.59)	.07	2.63 (0.91 – 7.59)	.07
	>$40,000	referent	referent	referent	referent
Smoking Status:	Current smoker	1.87 (0.89 – 3.93)	.10	1.60 (0.93 – 2.73)	.09
	Ex smoker	1.20 (0.50 – 2.84)	.68	0.30 (0.12 – 0.75)	.01
	Non smoker	referent	referent	referent	referent
Marital Status:	Never married	1.97 (0.87 – 4.47)	.10	7.92 (4.41 – 14.22)	<.001
	Divorced/separated/widowed	1.57 (0.81 – 3.05)	.18	5.26 (3.08 – 9.00)	<.001
	Married	referent	referent	referent	referent
Physical Illness	Yes	1.61 (0.81 – 3.22)	.17	2.26 (1.35 – 3.82)	.002
diabetes/hypertension/cancer or CHD	No	referent	referent	referent	referent