Abstract

Objectives: The aim of these analyses was to examine the association of cortisol, DHEAS and the cortisol:DHEAS ratio with the metabolic syndrome (MetS) and its components.

Design: The analyses were cross-sectional.

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. MetS was ascertained from data on body mass index; fasting blood glucose or a diagnosis of diabetes; blood pressure or a diagnosis of hypertension; high-density lipoprotein cholesterol; and triglyceride levels. Contemporary morning fasted cortisol and DHEAS concentrations were determined. The outcomes were MetS and its components. Analysis was by logistic regression, first adjusting for age and then additionally for an array of candidate confounders.

Results: Cortisol, although not in the fully adjusted analysis, and DHEAS were both related to MetS. Whereas high cortisol concentrations were associated with an increased risk of MetS, high DHEAS concentrations appeared protective. By far, the strongest associations with MetS were observed for the cortisol:DHEAS ratio; the higher the ratio, the greater the risk of having MetS. The ratio was also significantly related to four of the five MetS components.

Conclusions: The cortisol:DHEAS ratio is positively associated with MetS. Prospective analyses are needed to help untangle direction of causality, but this study suggests that the cortisol:DHEAS ratio is worthy of further study in this and other health contexts.

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Introduction

The metabolic syndrome (MetS) is a cluster of symptoms (obesity, high triglycerides, low high-density lipoprotein (HDL) cholesterol, raised blood pressure, and high fasting blood glucose or a diagnosis of diabetes) that increase the risk of cardiovascular and all-cause mortality (1–4). It is estimated that one quarter of the world’s adult population has the MetS (5). The overlap between presenting clinical features of MetS and Cushing’s disease has prompted the hypothesis that elevated cortisol may have an aetiological role in the development of MetS (5, 6). Indeed, circulating cortisol concentrations are higher in individuals with MetS and its components (7–11). However, some studies have reported no association between cortisol and MetS (12, 13).

There is even less consensus about whether DHEAS, the most abundant steroid in the human circulation, is implicated in MetS. Some data suggest that lower DHEAS concentrations characterize individuals with MetS (14), but, again, this is not a universal observation (12, 13). In addition, no studies have examined the cortisol:DHEAS ratio in this context. Both cortisol and DHEAS are synthesized within the adrenal cortex, and it is conceivable that their respective relative contributions to adrenal steroid output might define observed biological action. Furthermore, the cortisol: DHEAS ratio has been found to predict health outcomes better than the level of either hormone alone (15) as well as predicting all-cause mortality (16). Given the absence of data for the cortisol:DHEAS ratio, the variable outcomes for cortisol and DHEAS, and the importance of establishing the pathways leading to MetS, the present analyses of data from a substantial cohort of Vietnam era US veterans addressed the issue of whether cortisol and DHEAS, and their ratio are associated with MetS.
**Materials and methods**

**Sample**

Participants were male Vietnam era military veterans recruited as part of the Centers for Disease Control Vietnam Experience Study (17). The effective sample size was 4255. Ethical approval for the study was given by various bodies, including the US Centers for Disease Control, and participants gave informed consent. Details of sampling at each stage of data collection are described in detail elsewhere (17). Inclusion criteria were: entered military service between January 1 1965 and December 31 1971; served only one term of enlistment and at least 16 weeks of active duty; earned a military specialty other than ‘trainee’ or ‘duty soldier’; had a military pay grade at discharge no higher than sergeant.

**Data collection**

Information on place of service and ethnicity was extracted from the military archives. From a telephone survey in 1985, socio-economic position was measured using household income in midlife and the grade from which participants left school. Alcohol consumption, smoking habits and marital status were ascertained using standard questions. In 1986, participants underwent a thorough medical examination. Mean age at medical examination was 38.3 years (range: 31.1–49.0). Participants fasted from 1900 h on the previous evening until blood was drawn the following morning. Cortisol and DHEAS were assessed in 1986 from serum using a double antibody RIA system (Leeco Diagnostics, Inc., Southfield, MI, USA). From the fasted blood sample, triglycerides and cholesterol fractions were assessed using a Kodak Ektachem 700 autoanalyzer (18, 19). Serum glucose level was determined with an adaptation of the glucose oxidase-peroxidase-chromogen-coupled system (18, 19). Blood pressure was measured twice in the right arm using a sphygmomanometer and an aneroid. In 1986, participants went a thorough medical examination. Mean age at medical examination was 38.3 years (range: 31.1–49.0). Participants fasted from 1900 h on the previous evening until blood was drawn the following morning. Cortisol and DHEAS were assessed in 1986 from serum using a double antibody RIA system (Leeco Diagnostics, Inc., Southfield, MI, USA). Cortisol and DHEAS were assessed in 1986 from serum using a double antibody RIA system (Leeco Diagnostics, Inc., Southfield, MI, USA). Cortisol and DHEAS were assessed in 1986 from serum using a double antibody RIA system (Leeco Diagnostics, Inc., Southfield, MI, USA).

**Statistical analysis**

Cortisol, DHEAS and cortisol:DHEAS ratio values were not normally distributed, so they were natural logarithm-transformed. Demographic, service, health behaviour, metabolic and haemodynamic variables were compared between those with and without MetS using χ² and ANOVAs. Logistic regression was used to examine the relationships between cortisol, DHEAS, their ratio and MetS, first in age-adjusted analyses and then in fully adjusted analyses with the additional covariates of place of service, ethnicity, marital status, alcohol consumption, smoking, household income and education grade. Further fully adjusted regression models were tested in which both cortisol and the cortisol:DHEAS ratio were entered in one case and DHEAS and the cortisol:DHEAS ratio in the other. The association between the cortisol:DHEAS ratio and the individual MetS components was examined in further fully adjusted models. Linear regression, with full adjustment, was used to test the relationship between the ratio and the number of MetS components that participants possessed.

**Results**

Five hundred and eighty-four (14%) of the men were identified as having MetS. Aside from differing on all the components of MetS, participants with MetS were slightly older, tended to have a briefer education, were less likely to be divorced, widowed or separated and more likely to come from ethnic groups other than white or black (Table 1).

In age-adjusted logistic regression analyses, men with higher morning cortisol levels were more likely to exhibit MetS, odds ratio (OR)=1.35, 95% confidence interval (CI) 1.01–1.81, P=0.04. Higher DHEAS, on the other hand, was associated with significantly reduced incidence of MetS, OR=0.55, 95% CI 0.45–0.68, P<0.001. Those with higher cortisol: DHEAS ratios were much more likely to meet the criteria for MetS, OR=1.75, 95% CI 1.47–2.09, P<0.001. This association between the cortisol:DHEAS ratio and MetS is illustrated in Fig. 1, which shows a clear dose–response relationship. In the fully adjusted analyses, the association between cortisol and MetS was no longer statistically significant at conventional levels, OR=1.31, 95% CI 0.98–1.76, P=0.07. However, higher DHEAS concentrations were still negatively, OR=0.56, 95% CI 0.46–0.69, P<0.001, and the cortisol:DHEAS ratio still positively, OR=1.72, 95% CI 1.44–2.05, P<0.001, related to MetS. In fully and mutually adjusted models, the first entering both cortisol and the cortisol:DHEAS ratio and the second entering DHEAS and the cortisol:DHEAS ratio, only

0.98. Bench controls yielded coefficients of variation that were all <10%. Finally, current medication status was also determined at the medical examination.
the ratio emerged as a significant predictor of MetS, OR = 1.83, 95% CI 1.50–2.25, P < 0.001 and OR = 1.46, 95% CI 1.09–1.96, P = 0.01 respectively. The statistics for cortisol and DHEAS in these models were OR = 0.79, 95% CI 0.57–1.11, P = 0.18 and OR = 0.79, 95% CI 0.57–1.11, P = 0.18 respectively.

The cortisol:DHEAS ratio was also significantly associated with the number of components of MetS that a participant possessed, \( \beta = 0.12, t = 7.86, P < 0.001, R^2 = 0.014 \). Finally, of the components of MetS, the cortisol:DHEAS ratio was positively and significantly associated with high blood pressure, OR = 1.39, 95% CI 1.20–1.60, \( P < 0.001 \); high blood glucose, OR = 1.68, 95% CI 1.43–1.98, \( P < 0.001 \); high triglycerides, OR = 1.87, 95% CI 1.59–2.19, \( P < 0.001 \); and low HDL, OR = 1.19, 95% CI 1.04–1.35, \( P = 0.009 \), in fully adjusted models. The association between the cortisol:DHEAS ratio and obesity was only a trend, OR = 1.17, 95% CI 0.98–1.41, \( P = 0.09 \). When these fully adjusted analyses were rerun with adjustment for obesity, the cortisol:DHEAS ratio remained significantly associated with high blood pressure, OR = 1.38, 95% CI 1.19–1.59, \( P < 0.001 \); high triglycerides, OR = 1.88, 95% CI 1.60–2.21, \( P < 0.001 \); low HDL OR = 1.17, 95% CI 1.02–1.33, \( P = 0.02 \); and high blood glucose, OR = 1.67, 95% CI 1.41–1.97, \( P < 0.001 \).

### Table 1 Characteristics of participants with and without metabolic syndrome.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metabolic syndrome (n=584)</th>
<th>Non-metabolic syndrome (n=3671)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± S.D.</strong></td>
<td><strong>Mean ± S.D.</strong></td>
<td><strong>Mean ± S.D.</strong></td>
<td><strong>Mean ± S.D.</strong></td>
</tr>
<tr>
<td><strong>Metabolic syndrome markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.73 ± 4.15</td>
<td>25.17 ± 3.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.56 ± 2.43</td>
<td>1.09 ± 0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>0.89 ± 0.20</td>
<td>1.19 ± 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133.33 ± 12.50</td>
<td>121.36 ± 11.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>91.85 ± 9.29</td>
<td>82.88 ± 8.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>5.93 ± 1.71</td>
<td>5.13 ± 0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Predictor variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at medical examination (years)</td>
<td>38.74 ± 2.52</td>
<td>38.26 ± 2.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Units of alcohol per week</td>
<td>7.28 ± 16.78</td>
<td>7.05 ± 14.01</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
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<tr>
<td>Place of service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever in Vietnam</td>
<td>339 (58)</td>
<td>2009 (55)</td>
<td>0.32</td>
</tr>
<tr>
<td>Other overseas</td>
<td>142 (24)</td>
<td>953 (26)</td>
<td>0.03</td>
</tr>
<tr>
<td>US only</td>
<td>103 (18)</td>
<td>709 (19)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>473 (81)</td>
<td>3017 (82)</td>
<td>0.03</td>
</tr>
<tr>
<td>Black</td>
<td>60 (10)</td>
<td>435 (12)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>51 (9)</td>
<td>219 (6)</td>
<td></td>
</tr>
<tr>
<td>Household income in midlife</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20 000</td>
<td>183 (31)</td>
<td>1018 (28)</td>
<td>0.11</td>
</tr>
<tr>
<td>– $40 000</td>
<td>289 (50)</td>
<td>1840 (50)</td>
<td></td>
</tr>
<tr>
<td>&gt; $40 000</td>
<td>112 (19)</td>
<td>813 (22)</td>
<td></td>
</tr>
<tr>
<td>Years in education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 11</td>
<td>93 (16)</td>
<td>419 (11)</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>218 (37)</td>
<td>1346 (37)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>146 (25)</td>
<td>936 (26)</td>
<td>0.64</td>
</tr>
<tr>
<td>Ex smoker</td>
<td>166 (28)</td>
<td>1043 (28)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>272 (47)</td>
<td>1699 (46)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>459 (79)</td>
<td>2672 (73)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated/widowed</td>
<td>79 (13)</td>
<td>688 (19)</td>
<td>0.006</td>
</tr>
<tr>
<td>Never married</td>
<td>46 (8)</td>
<td>314 (8)</td>
<td></td>
</tr>
</tbody>
</table>

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that it is the ratio of these two hormones that will
determine biological outcome in vivo (26). Moreover,
there are no reports of MetS suppressing DHEAS
production, supporting the notion that the direction
of causality is from a lower ratio to MetS. Both cortisol
and DHEA/DHEAS secretion are under the regula-
tory influence of pituitary ACTH, and excessive
glucocorticoid production will lead to a down-
regulation of ACTH, resulting in reduced DHEA
secretion, as frequently observed in patients with an
adrenal cortisol-producing adenoma. However, the
circulating cortisol levels measured in this cohort are
not unusually elevated. Thus, a suppressive influence
of cortisol on DHEAS secretion seems unlikely. It may also
be the case that both hormonal profile and susceptibility
to MetS reflect programming effects in early life
consequent on prenatal resource deprivation (6). However,
the findings may not be able to be generalized to the
women and older populations. However, the sex
hormone binding globulin has been found to be
associated with MetS in both sexes (12, 13). None-
thless, as premenopausal women have slightly higher
total cortisol values and lower circulating DHEAS (27),
it would be interesting to examine the influence of the
cortisol:DHEAS ratio and MetS in women where the
relationship could be even stronger. The relative youth
of our sample is most likely the reason for the relatively
low prevalence of MetS. However, given that the
prevalence of MetS is generally higher in older
individuals (28), it is possible that the associations
observed would be even stronger in an older sample. It is
also worth noting that the cortisol:DHEAS ratio
increases with age (29), thus it is likely to be an even
stronger predictor of MetS in an older sample. The
second possible limitation is the use of a single morning
measurement of serum cortisol and DHEAS. Cortisol
has a diurnal rhythm which would be best captured
through multiple measurements of the free active
fraction of cortisol, such as that which can be
determined through saliva sampling. Furthermore, the
most accurate assessment for silent hypercortisolism is
an overnight dexamethasone suppression test. However,
the timing of the present samples was fairly consistent
across participants. Furthermore, DHEAS concen-
trations remain stable throughout the day and reflect
the 24-h secretion of DHEA (30, 31).

In conclusion, the cortisol:DHEAS ratio was positively
associated with MetS and many of its components.
Prospective research is required to clarify the causal
direction of this relationship and inform future
intervention strategies. In addition, it would be
worthwhile examining the cortisol:DHEAS ratio in the
context of other health outcomes.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References