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Major depressive disorder, generalised anxiety disorder, and their comorbidity: Associations with cortisol in the Vietnam Experience Study

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Summary
Objectives: The aim of these analyses was to examine the association of cortisol, dehydroepiandrosterone sulphate (DHEAS), and the cortisol:DHEAS ratio with the diagnoses of major depressive disorder (MDD), generalised anxiety disorder (GAD), and their comorbidity.
Design: This was a cross-sectional study.
Methods: Participants were 4256 Vietnam era US army veterans. From military service files, telephone interviews, and a medical examination, occupational, socio-demographic, and health data were collected. One-year prevalence of MDD and GAD was determined through a diagnostic interview schedule based on the DSM-IV criteria. Contemporary morning fasted cortisol and DHEAS concentrations were determined. Analyses of covariance were run, first with adjustment for age and then additionally adjusting for a range of candidate confounders.
Results: In fully adjusted analyses, there was evidence of lower basal cortisol levels in individuals with MDD and co-morbid MDD and GAD than those with GAD alone or no diagnosis.
Conclusion: This suggests that MDD and its comorbidity can also be characterised by low as well as high cortisol levels. A profitable line of future research might be to examine cortisol and DHEAS levels in more representative samples including older participants and women with and without MDD, GAD, and other psychiatric diagnoses.

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Mental health disorders in the general population are common (Kessler et al., 2005a,b). In fact, an estimated 14% of the global disease burden has been attributed to such conditions as depression and anxiety (World Health Organisation, 1992–1994). This is likely to be an underestimate of the true burden of mental health problems as it fails to take into consideration that mental health increases the risk of other health conditions such as communicable and non-communicable diseases, and injuries (Prince et al., 2007). Populations who have been exposed to traumatic events, such as war veterans, have an even higher prevalence of major mental health problems, particularly depressive disorder (MDD) and generalised anxiety disorder (GAD) (Reeves et al., 2005; Gaylord, 2006; Hoge et al., 2006). For example, soldiers assessed a few months after returning from deployment to Afghanistan and Iraq had a GAD prevalence of around 14% and 15%, respectively, and prevalence of MDD of around 17% and 16% (Hoge et al., 2004). As yet, the aetiology of depression and anxiety are not fully understood, although it is generally accepted that chronic exposure to stressful life events has an important role (Thomson and Craighead, 2008).

The hypothalamic pituitary adrenal (HPA) axis is the major neuroendocrine stress response system. Abnormalities in HPA function have been observed in major depressive disorder and have been causally linked to such conditions (Schatzberg et al., 1985; Thomson and Craighead, 2008). A flattened diurnal rhythm for cortisol (Young et al., 1993), and elevated urinary and blood cortisol levels have been observed in several studies of individuals with depression (Lesch et al., 1988; Kathol et al., 1989; Deuschle et al., 1997; Burke et al., 2005). However, the general conclusion that the HPA axis is hyperactive in MDD is based primarily on evidence from provocative stress tests or the administration of dexamethasone (Holsboer et al., 1995). In contrast, studies of basal HPA axis hormone secretion in patients with depression have produced mixed results (Posener et al., 2004). Some have shown no evidence of hypercortisolism, but a more erratic pattern of secretion across the day (Yehuda et al., 1996; Peeters et al., 2004); others have found lower levels of cortisol among those with MDD (Vythilingam et al., 2004; Decker, 2006); and still others, have reported no difference in basal cortisol levels between depressives and controls (Porter et al., 2003). Thus, it seems that the HPA axis dysregulation in MDD is not always observed as hyperactivity.

Less is known about the association between MDD and dehydroepiandrosterone (DHEA), another adrenal cortex hormone. DHEA is a precursor of 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 (Sacco et al., 2002; Hazeldine et al., 2010). 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 (Butcher et al., 2005; Radford et al., 2010). Moreover, our recent studies have shown that DHEAS is able to increase neutrophil superoxide generation via direct activation of the protein kinase C signalling pathway and phosphorylation of NADPH oxidase (Radford et al., 2010). It also appears that the activity of the HPA axis as reflected in the ratio of cortisol to DHEAS is particularly important with regard to health. For example, the cortisol:DHEAS ratio has been found to predict health outcomes better than the level of either hormone alone (Butcher et al., 2005). However, few studies have examined the cortisol:DHEAS ratio in the context of mental disorders. Of the scant research considering the role of DHEA/S, two studies found that lower DHEA was related to MDD diagnosis (Goodyer et al., 1996; Michael et al., 2000). However, some researchers have shown higher DHEA (Heuser et al., 1998) and a higher cortisol:DHEA ratio (Young et al., 2002) among depressed adults whereas, others have found no difference in DHEA or the cortisol:DHEA ratio between those with and without MDD (Porter et al., 2003).

Post-traumatic stress disorder (PTSD) is another psychiatric diagnosis which has received much attention with regard to the stress of war exposure (Foy et al., 1987). Individuals with such a diagnosis have also been shown to exhibit alterations in HPA axis hormones, for example, lower cortisol levels have been observed in several studies of patients with PTSD (Yehuda et al., 1990, 1995; Mason et al., 2001). In contrast, increased levels of cortisol and DHEA (Pico-Alfonso et al., 2004), and higher DHEAS (Spivak et al., 2000; Sondergaard et al., 2002) have been observed in some patients with PTSD although some studies have observed lower levels of DHEAS (Kanter et al., 2001). MDD is often found to occur co-morbidly with PTSD (Resnick et al., 1993; Kessler et al., 1995; Gaudiano and Zimmerman, 2010), for example, a study of the lifetime prevalence of anxiety and mood disorders found that PTSD was the disorder most likely to be associated with MDD, with a 69% of individuals with PTSD also meeting the criteria for MDD (Brown et al., 2001). Further, in one sample of 677 depressed patients, 36% was also found to screen positive for PTSD (Campbell et al., 2007), and in another, rates of comorbidity of PTSD and MDD were 42% (DeRubeis et al., 2005). In fact, following trauma exposure, it is likely that the development of MDD and PTSD are often not independent (Breslau et al., 2000; O'Donnell and Wolffsohn, 2004). There is evidence that patients with both PTSD and MDD also exhibit lower cortisol levels than non-patients (Vythilingam et al., 2010). In the present veteran sample, lower cortisol has been shown among those with PTSD, and lower DHEAS among those with comorbidity of PTSD and MDD (Boscarino, 1996, 2004).

Despite the high prevalence of GAD, few investigators have examined the association between GAD and HPA axis hormones. Of the few studies specifically considering GAD, most have concentrated on cortisol, and showed higher cortisol levels in GAD patients than controls (Mantella et al., 2008; Hood et al., 2010), and higher cortisol levels in those with mixed anxiety–depressive disorder (Kara et al., 2000). As far as we are aware, no study has examined the association between GAD and DHEA/S, although DHEA supplementation has been shown to improve anxiety symptoms in patients with schizophrenia (Strous et al., 2003) but not in women with fibromyalgia (Finckh et al., 2005).

Given the reported high prevalence of GAD and MDD in army veterans and the significant prevalence of these disorders in the general population, their individual and combined association with HPA axis hormones merits research attention. Consequently, the present analyses examined the associations between GAD, MDD and their comorbidity and cortisol, DHEAS, and the cortisol:DHEAS ratio in a substantial cohort of US veterans from the Vietnam Experience Study. Given the equivocal findings from the research on MDD and cortisol, and the lack of previous data for GAD, no directional hypotheses were formulated.