



# DHEAS and cortisol/DHEAS-ratio in recurrent depression: State, or trait predicting 10-year recurrence?



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## KEYWORDS

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Remission;  
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## Summary

**Background:** Major depressive disorder (MDD) has been associated with low dehydroepiandrosterone-sulphate (DHEAS), – particularly relative to high cortisol – although conflicting findings exist. Moreover, it is unclear whether low DHEAS is only present during the depressive state, or manifests as a trait that may reflect vulnerability for recurrence. Therefore, we longitudinally tested whether low DHEAS and high cortisol/DHEAS-ratio in recurrent MDD (I) reflects a trait, and/or (II) varies with depressive state. In addition, we tested associations with (III) previous MDD-episodes, (IV) prospective recurrence, and (V) effects of cognitive therapy.

**Methods:** At study-entry, we cross-sectionally compared morning and evening salivary DHEAS and molar cortisol/DHEAS-ratio of 187 remitted recurrent MDD-patients with 72 matched controls. Subsequently, patients participated in an 8-week randomized controlled cognitive therapy trial. We repeated salivary measures after 3 months and 2 years. We measured clinical symptoms during a 10-year follow-up.

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**Results:** Remitted patients showed steeper diurnal DHEAS-decline ( $p < .005$ ) and a flatter diurnal profile of cortisol/DHEAS-ratio ( $p < .001$ ) than controls. We found no state-effect in DHEAS or cortisol/DHEAS-ratio throughout follow-up and no association with number of previous episodes. Higher morning cortisol/DHEAS-ratio predicted shorter time till recurrence over the 10-year follow-up in interaction with the effects of cognitive therapy ( $p < .05$ ). Finally, cognitive therapy did not influence DHEAS or cortisol/DHEAS-ratio.

**Conclusions:** Diurnal profiles of DHEAS and cortisol/DHEAS-ratio remain equally altered in between depressive episodes, and may predict future recurrence. This suggests they represent an endophenotypic vulnerability trait rather than a state-effect, which provides a new road to understand recurrent depression and its prevention.

**Trial registration:** [www.isrctn.com/ISRCTN68246470](http://www.isrctn.com/ISRCTN68246470).

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## 1. Introduction

Major depressive disorder (MDD) represents a large burden of disease, mainly due to its high recurrence and cardiovascular comorbidity risks (Assies et al., 2014; Bockting et al., 2005). Indicatively, 80% of recovered MDD-patients experience an average of five recurrences during lifetime (Bhagwagar and Cowen, 2008), and cardiovascular disease is a leading cause of death in MDD (Assies et al., 2014). If we better understand recurrent MDD's pathophysiology, we may improve prevention of recurrence and cardiovascular disease in at-risk patients.

An important pathophysiological characteristic of MDD is altered activity of the hypothalamic–pituitary–adrenal (HPA)-axis (Stetler and Miller, 2011). HPA-axis hormone cortisol has been extensively studied, and mainly found to be present in higher concentrations in MDD-patients (Stetler and Miller, 2011), which was also reported by our group in the present study's sample of patients with recurrent MDD (Lok et al., 2012). The potentially detrimental effects of chronic high cortisol has been termed allostatic load (McEwen, 2007), which may explain e.g. reduced hippocampal volumes and atherosclerosis, contributing to the extensive recurrence and cardiovascular comorbidity rates in MDD.

However, more abundantly than cortisol, adrenal glands also secrete the neuroactive steroids dehydroepiandrosterone (DHEA) and its sulfate ester DHEAS [jointly referred to as DHEA(S)] (Maninger et al., 2009). While DHEA(S)' precise role remains unclear, DHEA(S) is thought to counteract cortisol's effects on allostatic load (Maninger et al., 2009). Specifically, while cortisol has a catabolic function, DHEA(S) seems to have an anabolic, regenerative, and neuroprotective function in the brain and cardiovascular system (Maninger et al., 2009), which may be mediated through effects on brain derived neurotrophic factor (BDNF) and gamma-aminobutyric-acid (GABA)-metabolism (Genud et al., 2009; Sakr et al., 2014). Consequently, the cortisol/DHEA(S)-ratio is proposed to represent a balance between catabolic and anabolic activity (Chen et al., 2015; Lennartsson et al., 2013).

Although DHEA(S) derived far less attention in MDD compared to cortisol, an elevated cortisol/DHEAS-ratio has been found in MDD-patients and has been proposed as a state marker of MDD (Maninger et al., 2009; Young et al., 2002). However, opposite results of no differences or higher

DHEA(S) have also been reported (Assies et al., 2004; Maninger et al., 2009). These conflicting findings may be caused by the relatively small size and large heterogeneity of the investigated samples thus far (Maninger et al., 2009). Nevertheless, given DHEA(S)' anabolic effects (e.g. neuroprotection and regeneration), low DHEA(S) – particularly relative to cortisol – could be of clinical importance because it may intensify allostatic load and thereby contribute to recurrence and cardiovascular comorbidity in MDD (Juster et al., 2010). Therefore, assessment of DHEA(S) in addition to cortisol provides a more complete indication of HPA-axis functioning.

However, the precise characteristics of altered DHEA(S) in MDD remain unknown (Maninger et al., 2009). Using the sample of the present study, we previously suggested that high cortisol in MDD is a trait (indicating an endophenotype), not a state (epiphenomenon) (Lok et al., 2012). Whether this also holds true for DHEA(S) remains unknown, because of a lack of prospective repeated measures studies (Maninger et al., 2009). In addition, we observed that cortisol was relatively lower (suggesting HPA-axis blunting/exhaustion) in patients with more previous MDD-episodes (MDEs) (Lok et al., 2012). Other analyses in the recurrent MDD sample showed that cortisol predicted time to recurrence in interaction with cognitive therapy. In detail, while in remitted patients who did not receive cognitive therapy lower cortisol was associated with early recurrence; in patients who received cognitive therapy higher cortisol levels relatively predicted early recurrence (Bockting et al., 2012, 2006). Finally, we (Lok et al., 2012; based on analyses in the present study's sample) and others (Hsiao et al., 2011) found that psychotherapy resulted in steeper declines in diurnal cortisol. To the best of our knowledge, relations of these factors with DHEA(S) in MDD remain unclear.

Therefore, after examining the above relations in recurrent MDD for cortisol, we aimed to test the following hypotheses for DHEAS and cortisol/DHEAS ratio as well: (I) during remission DHEAS will be lower, and cortisol/DHEAS-ratio higher, than in never-depressed controls (suggesting a trait), (II) DHEAS or cortisol/DHEAS-ratio will not change during the depressive state, (III) more previous MDEs will be associated with lower DHEAS and a higher cortisol/DHEAS-ratio, (IV) higher DHEAS and lower ratio will predict longer time till prospective MDD-recurrence, and (V) psychotherapy will increase DHEAS and decrease the cortisol/DHEAS-ratio.

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