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**Immune-endocrine biomarkers associated with mental health: a 9-year longitudinal investigation from the Hertfordshire Ageing Study**

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**Abstract**

*Background:* The study of neural-endocrine-immune system interactions has led to substantial advances in our understanding of neuropsychiatric disorders. Growing evidence reveals the pivotal roles of inflammatory cytokines signalling the brain to produce neurochemical, neuroendocrine, and neuroimmune changes which affect mood and behaviour. Ageing is accompanied by the development of low-grade systemic inflammation which may promote changes in the neural systems predisposing to geriatric depression via the hypothalamic-pituitary-adrenal (HPA) axis. The aim of this study was to investigate the longitudinal associations between baseline values and conditional changes (independent of baseline) in immune-endocrine biomarkers and mental health status in a population-based cohort of older adults.

*Methods:* Data from 347 subjects (200 men, 147 women) who participated in the Hertfordshire Ageing Study at baseline (1994/5, mean age 67.3 years) and at 9-year follow-up were analysed. Serum samples for analysis of inflammatory and endocrinological measures were collected at baseline and follow-up. At follow-up, depression (Hospital Anxiety and Depression Scale) and mental health (Short Form-36 questionnaire) were assessed. Baseline values and changes in biomarkers in relation to risk of high depression scores (top sex-specific third) and low mental health scores (bottom sex-specific third) were examined using logistic regression.

*Results:* Lower baseline cortisol was related to greater risk of high depression scores; higher baseline cortisol: Dehydroepiandrosterone Sulphate ratio (men only) and higher baseline C-reactive protein (CRP) (women only) were related to greater risk of poor mental health scores. In addition, greater decline in cortisol was related to increased risk of high depression scores among men. These relationships were robust (p<0.05) after controlling for sex, age, BMI, smoking, alcohol consumption and number of systems medicated.

*Conclusion:* This study provides further evidence of the role of the HPA and inflammation in older adults with poor mental health. In addition, the findings highlight sex differences where increased inflammation in women and declines in cortisol in men was linked to poorer mental health. Further research is warranted to confirm these findings. This could lead to the search for potential biomarkers to stratify medications as well as developing novel intervention targets to improve mental health at older age.

**Keywords:** Psychoneuroimmunology,Inflammation, The hypothalamic-pituitary-adrenal axis, C-reactive protein, Cortisol, Mental health, Depression

**1 Introduction**

Research into psychoneuroimmunology, the study of neural-endocrine-immune system interactions, has led to substantial advances in our understanding of neuropsychiatric disorders (Ader et al., 1995; Raison et al., 2006; Leonard and Myint, 2009; Miller et al., 2009). Experimental and clinical research reveals the pivotal roles of inflammatory cytokines signalling the brain to produce neurochemical, neuroendocrine, and neuroimmune changes which lead to mood and behavioural changes. Ageing is accompanied by the development of low-grade systemic inflammation due to increasing stressors resulting from declining physical health and diminishing social connections (Prasad et al. 2012; Jeon and Dunkle 2009). With a rapidly ageing global population, there is an urgent need to advance our understanding of the pathobiological mechanisms underlying poor mental health at older ages.

The hypothalamus–pituitary–adrenal (HPA) axis plays a fundamental role as a regulatory system in stress responses and inflammation. Alteration of the HPA axis is observed in a significant proportion of patients with major depression and seems to reflect an impaired ability of cortisol to exert its physiological effects including the negative feedback on the HPA axis itself as well as the anti-inflammatory effects at the peripheral level (Pariante, 2006; Pariante and Miller, 2001). Growing evidence supports the role of the HPA hyperactivity and inflammation in the aetiology and pathogenesis of depression in younger adults (Malhi and Mann 2018; Iob et al. 2020) indicated by elevated cortisol levels (Stetler and Miller 2011) and higher concentrations of pro-inflammatory cytokines such as IL-6 and C-reactive protein (CRP) (Haapakoski et al. 2015). However, ﬁndings of these biological disturbances in late life depression have been divergent due to greater heterogeneity of depression in older adults and the complexity of the ageing process.

Longitudinal studies are crucial in understanding whether immune-endocrine biomarkers are predictors, correlates or consequences of poor mental health. One recent meta-analysis suggests that both CRP and IL-6 were associated with future depressive symptoms (Mac Giollabhui et al. 2020). The English Longitudinal Study of Ageing (ELSA) found high CRP levels at baseline (mean age 64.7) associated with depressive symptoms at the 4-year follow-up (Au et al. 2015). Evidence also indicates dysregulated inflammatory processes in older depression patients, which further supports the inflammatory hypothesis of geriatric depression (Alexopoulos and Morimoto 2011). Building on our previous work of age-related increase in low-grade systemic inﬂammation identified in the Hertfordshire Ageing Study (HAS) cohort (Bartlett et al. 2012), the present study aimed to further investigate how inflammation and the HPA dysregulation contribute to mental health state 9-years later in the same cohort of older adults. We hypothesised that the HPA dysregulation and low-grade inflammation may contribute to poor mental health in late life. In addition, based on converging evidence from animal and human studies demonstrating sex differences in the immune response to stress and the HPA disturbance, we expected that there would be strong sex differences. Findings from the study have important neuropsychopharmacological implications by revealing targets for potential therapeutic development as well as informing strategies for the prevention of poor mental health in at-risk populations.

**2 Methods**

*2.1 Study population*

The HAS is a birth cohort study established to investigate the lifecourse determinants of ageing which has been described in detail previously (Sayer et al. 1998). From 1911 to 1948, midwives collected detailed records on infants born in Hertfordshire, UK. There were 6,803 live singletons born in North Hertfordshire between 1920 and 1930. With the help of the National Health Service Central Register, 1,428 who still lived there in 1994 were traced and 824 (58%) of the traced people agreed to a home interview. Information on medical history and lifestyle was obtained. After interview, 717 men and women attended a clinic for detailed characterisation of ageing in a range of systems. In total, 359 men and women completed a 9-year follow-up home interview and 294/359 (82%) participants attended a clinic for a further assessment of their health. See details about the HAS recruitment in the cohort profile by Syddall et al. (2010).

The study had ethical approval from the Hertfordshire and Bedfordshire Local Research Ethics Committee and all participants provided written informed consent.

*2.2 Ascertainment of participant characteristics at baseline (1994/5)*

At the home interview, a trained research nurse ascertained smoking status, alcohol consumption and medication use. At the baseline clinic, height and weight were measured. Details of all currently used over-the-counter or prescription medications were coded to the British National Formulary (BNF). These medications were then categorised into the following body systems corresponding to chapters of the BNF: cardiovascular; respiratory; gastro-intestinal; endocrine; central nervous; malignant disease and immunosuppression; nutrition and blood; musculoskeletal and joint disease; eye; ear; nose; skin; miscellaneous; and genito-urinary tract. The number of systems each participant was taking medications for was calculated and used as an ordinal variable in analyses.

*2.3 Ascertainment of biomarkers at baseline clinic (1994/5) and follow-up clinic (2003/5)*

A venous blood sample was collected and serum was aliquoted and stored at −80°C for future analysis. Serum was thawed and the serum-free cytokines IL-1β, IL-6, IL-10 and TNF-α were simultaneously measured using commercially available multiplex luminometry (BioRad Ltd, Hemel Hempstead, UK); intra-assay coefficients of variation of 7.15 to 13.89 for these biomarkers using these assays have been reported previously (Duggal et al. 2013). C-reactive protein (CRP) was measured using singleplex luminometry (Invitrogen, UK). Samples were analysed on a Luminex 100 instrument (Luminex Corp., Austin, TX, USA) with the acquisition software StarStation (Applied Cytometry Systems, Sheffield, UK) (Bartlett et al. 2012). Detection of serum cortisol and Dehydroepiandrosterone Sulphate (DHEAS) was completed using commercially available enzyme-linked immunosorbent assay kits (IBL International, Germany)(see details in Baylis et al. 2013). Intra-assay coefficients of variation of 6.7 for cortisol and 4.6 for DHEAS regarding these assay kits have been reported previously (Duggal et al. 2013).

*2.4 Assessment of mental health status at follow-up interview (2003/5)*

Depression and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983). This scale uses two separate subscales to assess symptoms of depression and anxiety with scores ranging from 0-21 for each subscale; higher scores indicate more severe symptoms. Scores of 8-10 and ≥11 are used to diagnose possible and probable depression/anxiety respectively. Health-related quality of life was assessed using the Short Form-36 (SF-36) questionnaire (Ware and Gandek 1998); a participant’s responses to 36 questions were mapped onto 8 domains. Data from the HADS depression scale and the SF-36 mental health domain were used in this study.

*2.5 Derived variables*

Height (m) and weight (kg) were used to derive BMI (kg/m2). Number of systems medicated was calculated from medication use. Biomarkers were positively skewed and were therefore log- or square-root transformed. Conditional changes (independent of baseline) in each biomarker were characterised by residuals from sex-specific linear regression models for the biomarker at follow-up on the baseline biomarker with adjustment for individual follow-up duration. High depression scores (>3 [men], >4 [women]) were regarded as those in the highest sex-specific third of the distribution; low mental health scores (<77 [men], <68 [women]) were those in the lowest sex-specific third of the distribution.

*2.6 Statistical analysis*

Participant characteristics were described using summary statistics. Baseline values and conditional changes in each biomarker in relation to risk of high depression scores and low mental health scores at follow-up were examined using sex-adjusted and sex-stratified logistic regression models. All models were adjusted for baseline age and fully-adjusted models also accounted for baseline BMI, smoking status (ever vs never), alcohol consumption and number of systems medicated. Models for baseline biomarkers as exposures were also adjusted for follow-up time.

The analysis sample comprised the 347 participants who had data on HADS depression or SF-36 mental health scores in 2003/5 and who also had data on at least one baseline inflammatory marker in 1994/5. A subset of these 347 participants also had data on changes in biomarkers from 1994/5 to 2003/5; information on the number of participants with data on each characteristic is presented in Table 1. Data analyses were conducted using Stata, release 15.1 (StataCorp, College Station, TX, USA).

**3 Results**

*3.1 Participant characteristics of the analysis sample*

Characteristics of the 347 HAS participants who were included in the analysis sample are presented in Table 1. Mean (SD) age at baseline was 67.3 (2.2) years; Median (lower quartile, upper quartile) follow-up time was 9.3 (8.9, 9.6) years. Median (lower quartile, upper quartile) scores for mental health status at follow-up were as follows: HAD depression [men: 3 (1, 5), women: 3 (1, 6)] and SF-36 mental health (men: 84 (72, 92), women: 76 (64, 88)]. Median DHEAS values at baseline were higher among men (862.9 ng/ml) than women (577.5 ng/ml) and declined over the follow-up period among both sexes. In contrast, average cortisol levels increased over time. High values of IL-1β were reported at baseline: median (lower quartile, upper quartile) values of 11.3 (5.6, 17.7) pg/ml among men and 16.3 (11.7, 26.9) among women. Spearman correlations between Il-6 and CRP were 0.13 among men and 0.36 among women; spearman correlations of 0.50 among men and 0.46 among women were observed between IL-1B and TNFa. Sex-specific correlations between all biomarkers at baseline are presented in Supplementary Table 1.

*3.2 Baseline biomarkers in relation to HAD depression and SF-36 mental health scores at follow-up*

Risk of high HAD depression and poor SF-36 mental health scores at follow-up according to baseline values of biomarkers are presented in Table 2 and Figure 1. In the pooled analysis and among women, lower baseline cortisol was related to greater risk of high depression scores. Among women, higher baseline CRP was related to greater risk of poor mental health scores. Among men, higher baseline cortisol: DHEAS ratio was associated with increased risk of poor mental health scores. These associations were robust after accounting for sex, age and follow-up time and in fully-adjusted analysis. Among men, lower baseline DHEAS was related to increased risk of poor mental health scores after adjustment for age and follow-up time (p=0.03) but this association was borderline significant (p=0.06) in fully-adjusted analysis.

*3.3 Longitudinal changes in biomarkers in relation to HAD depression and SF-36 mental health scores at follow-up*

Risk of high HAD depression and poor SF-36 mental health scores at follow-up according to longitudinal changes in biomarkers from baseline to follow-up are presented in Table 3 and Figure 1. Among men, greater decline in cortisol was related to increased risk of high depression scores after adjustment for age and in fully-adjusted analysis. Among women, longitudinal increases in IL-6 were related to greater risk of poor mental health scores in fully-adjusted analysis (p=0.04); this association was borderline significant (p=0.05) after adjustment for only age.



**Figure 1: Odds ratios (95% CI) for high depression and poor mental health scores at follow-up per standard deviation difference in baseline biomarker and per standard deviation increase in biomarker from baseline to follow-up**

Cor:DH: Cortisol:DHEAS ratio; CI: Confidence interval

Estimates in black are based on the pooled sample of men and women with adjustment for sex.

Estimates in dark grey are based on the sample of men only.

Estimates in light grey are based on the sample of women only.

Odds ratios were adjusted for baseline age, BMI, smoking history, alcohol consumption and number of systems medicated; models with baseline biomarkers as exposures were also adjusted for follow-up time.

High depression scores were those in the highest sex-specific third of the distribution. Poor mental health scores were those in the lowest sex-specific third.

Conditional changes in biomarkers from baseline to follow-up were derived using a residual change approach and were independent of baseline values.

Odds ratios are shown by circles; triangles represent odds ratios that were statistically significant (p<0.05).

**4 Discussion**

Longitudinal data from the HAS cohort revealed significant impact of HPA dysregulation on poor mental health over a 9-year follow-up period, in particular, lower baseline cortisol was related to higher HAD depression scores 9 years later among the pooled sample of men and women. Sex-stratified analysis indicated significant associations between increased inflammation and poorer SF-36 mental health scores in women whereas a significant association between decline in cortisol level and higher HAD depression scores in men was observed. This study provides further evidence of the role of the HPA and inflammation in older adults with poor mental health. In addition, the findings highlight different roles the HPA and inflammation may play in the aetiology and pathophysiology of mental health state in older men and women.

Previous studies have examined inﬂammation and cortisol measures in the older depressed population (Bremmer et al. 2007; Belvederi Murri et al., 2014; Martinez et al., 2016). However, there have been inconsistent findings on cortisol measures. Some studies reported higher cortisol levels (Balardin et al., 2011; Kuo et al., 2011; Belvederi Murri et al., 2014; Rhebergen et al., 2015), whereas other studies found hypoactivity of the HPA axis and hypocortisolism associated with late-life depression (Morrison et al., 2000; Oldehinkel et al., 2001). Studies suggested that physical frailty and exhaustion might underly HPA axis insufficiency (Fries et al., 2005, Morrison et al., 2001, Oldehinkel et al., 2001). Some studies also reported a U-shaped association between cortisol and depression in older adults (Bremmer et al., 2007; Penninx et al., 2007). Some data seem to suggest that depression in older adults is associated with an imbalance of the stress response, resulting in either hypocortisolemia or hypercortisolemia, depending on individual characteristics. Some argue these inconsistent findings may be due to greater heterogeneity of depression in older adults, however, this was not supported by the study by Veltman et al. (2018) who did not detect any diﬀerences in inﬂammation and cortisol measures between depression subtypes in older adults.

In the current study, relatively lower baseline cortisol in the pooled sample of men and women was associated to higher depression scores at the follow-up. This counter-intuitively supports HPA axis hypoactivity instead of hyperactivity. The potential causes for changes in HPA axis activity to hypocortisolaemia can be attributed to a failure in self-adjusting abilities of the body to enduring increased glucocorticoids, a form of over-adjustment (Fries et al., 2005). A likely cause may be due to the increased sensitivity and responsiveness of the HPA axis to negative feedback, as found in patients with PTSD and stress-related disorders (Yehuda, 1997, Heim et al., 1998). Deficiency in enzymes controlling cortisol catabolism can also lead to reduced cortisol clearance, and hence less free cortisol is required as peripheral degradation is attenuated (Yehuda et al., 2011). Other possible causes include reduced biosynthesis or depletion of CRH and ACTH; or due to hypersecretion of one of these, followed by consequent downregulation of the target receptor (Heim et al., 2000). Such reasons for a hyporeactive HPA axis under prolonged stress are likely to contribute to basal hypocortisolaemia. However, it should be noted that the cortisol level detected in this study is only relatively low and more evidence is needed to confirm hypocortisolaemia in this population. Further research is also warranted to sufficiently elaborate these potential mechanisms underlying hypocortisolaemia in chronic stress and depression. DHEAS is an ACTH-regulated steroid that possesses anti-glucocorticoid properties and any disruption of the dynamic balance between DHEAS and cortisol may increase the risk of poor mental health (Kalimi et al. 1994; Kamin and Kertes, 2017). Sex-stratified analysis revealed that higher baseline cortisol:DHEAS ratio, driven by lower baseline DHEAS, was associated with poorer mental health scores among men at follow-up. This is in line with findings from the ELSA study and further supports that higher serum DHEAS protects against the onset of depression in the elderly (Souza-Teodoro et al. 2016). In addition, the current study also found that greater declines in cortisol predicted higher depression scores in men, indicating reduced cortisol bioavailability and attenuated glucocorticoid responsiveness. However, these associations were absent in women which highlights stronger contribution of the HPA disturbance to poor mental health in men than in women. This indicates sex differences in terms of biological mechanisms underlying poor mental health. Furthermore, sex-differences in mean DHEAS levels may limit the utility of this biomarker and the cortisol:DHEAS ratio as a predictor of ageing and psychological status; sex-specific thresholds for these biomarkers may need to be ascertained in light of this.

Low-grade systemic inﬂammation, characterized by increased levels of serum C-reactive protein (CRP) and pro-inflammatory cytokines, has been identified in the HAS cohort (Bartlett et al. 2012). However, the longitudinal associations between these inflammatory markers and mental health state have not been examined before. CRP is a commonly used marker of inflammation and elevated levels of CRP have been associated with increased risk of psychological distress and depression in a large population study (Wium-Andersen et al. 2013). While these associations in the pooled sample of men and women were not statistically significant, sex-stratified analysis revealed that higher baseline CRP was related to poorer mental health scores in women 9 years later suggesting higher inflammation may lead to poorer mental health in women. The underlying mechanism could be that the immune disturbance can influence the activity of enzymes controlling tryptophan which lead to disturbed neuroregulation involved in emotion and behaviour such as decreased production of serotonin and increased production of kynurenic and quinolinic acids (Capuron and Miller 2011; Haroon et al. 2012). It should be noted that the relatively high levels of IL-1β in both men and women were observed at baseline in the current study. However, no associations were detected between IL-1β and depression/mental health scores. Despite relatively low levels of IL-6 observed at baseline, sex-stratified analysis revealed that longitudinal increases in IL-6 were related to poorer mental health scores among women which supports the same association reported in the meta-analysis reviewing inflammatory markers associated with late-life depression (Martínez-Cengotitabengoa et al., 2016). However, this association in HAS was borderline significant (p=0.05) when only adjusted for age. In the current study, these associations were absent in men which suggests that women may be more vulnerable to the effects of inflammation on their mental health than men. Sex is a biological variable that affects the functions of the immune system including both innate and adaptive immune responses throughout life (Klein and Flanagan 2016). Research has also shown that women appear to be more affected by risk factors that elevate inflammation, including childhood adversity, somatic symptomatology, relationship distress, obesity, physical inactivity, and nutrition status and the composition of the microbiome. Sex differences are also supported by evidence examining the neuro-immune consequences of stress, in particular, chronic stress leads to a greater suppression of cell-mediated immunity in women than in men (Bekhbat and Neigh 2018). Therefore, women’s susceptibility to inflammation and its risk factors may contribute to the sex differences found in the HAS cohort.

It should be noted that there are several limitations in this study. First, there may be reporting bias due to self-reported measures of mental health status. Second, lack of information is available on baseline mental state measures, duration of mental health status and prior mental health conditions. Third, the HAS is a population-based study with a low prevalence of clinical depression (6/347 participants in the analysis sample were taking antidepressants at baseline and 13/347 were taking antidepressants at follow-up) which may limit the comparability of findings from HAS with those from clinical population studies. Similarly, few participants had elevated biomarker levels or depression scores that would be expected among clinical patients. This is unsurprising as HAS is a community-dwelling cohort where a healthy participant effect has been identified (Syddall et al. 2010). Therefore, clinically relevant thresholds for levels of biomarkers and depression/mental health scores were not used. Instead, general trends of greater risks of high depression scores and low mental health scores according to baseline levels and longitudinal changes in biomarkers were reported; high depression scores were regarded as those in the highest sex-specific third of the distribution and low mental health scores were those in the lowest sex-specific third of the distribution. Fourth, this study was exploratory and used a relatively small sample size, especially for the sex-specific analyses. Fifth, the sample size for successfully assayed biomarkers differed between participants; a consequence of this is that different numbers of non-missing values were available for different biomarkers. Finally, information relating to additional potential confounding factors such as stress level, inflammatory events, physical activity levels, and sleep patterns were unavailable. Although psychosocial factors such as history of maltreatment, early life adversity, chronic fatigue syndrome and job burnout may have predisposed participants to lower HPA activity, it was not possible to account for these factors as they were not available in this cohort. Similarly, we cannot exclude the possibility that the observed associations could have been driven by various chronic or physical illnesses at baseline. However, the reported relationships were robust to adjustment for number of systems medicated at baseline, a marker of morbidity burden that has been used previously in HAS (Syddall et al. 2017; Syddall et al. 2010). Furthermore, measures of morbidity burden based on medication use are widely used and are strongly predictive of health outcomes (Huntley et al. 2012).

**5 Conclusions**

The HAS cohort offers the opportunity of examining the associations between immune-endocrine biomarkers and mental health state in older adults over a 9-year follow-up period. Data from the sex-pooled analysis suggests that low baseline cortisol level predicts greater risk of depression 9 years later. In addition, the findings highlight sex differences in the effects of inflammation and HPA function on mental health where increased inflammation in women and declines in cortisol in men were linked to poorer mental health state. Further research is warranted to confirm these findings. This could lead to the search for potential biomarkers to stratify medications as well as developing novel intervention targets to improve mental health at older age.

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| **Table 1: Descriptive statistics of the analysis sample** |
|  |  |  |  |
| **Characteristic [Mean (SD), Median (lower quartile, upper quartile) or N(%)]** | **Men (n=200)** | **Women (n=147)** | **Obs** |
|
| ***Baseline (1994/5)*** |  |  |  |
| Age (years) | 67.2 (2.3) | 67.3 (2.1) | 347 |
| Height (cm) | 172.6 (6.3) | 159.3 (5.5) | 347 |
| Weight (kg) | 80.8 (12.4) | 69.3 (11.3) | 347 |
| BMI (kg/m2) | 27.1 (3.5) | 27.3 (4.3) | 347 |
| Ever smoked regularly | 146 (73.0%) | 80 (54.4%) | 347 |
|  |  |  |  |
| Weekly alcohol units |  |  |  |
|  Non-drinker | 44 (22.0%) | 72 (49.0%) | 347 |
|  Low (1-10 [M], 1-7 [W]) | 104 (52.0%) | 63 (42.9%) |
|  Moderate (11-21 [M], 8-14 [W]) | 31 (15.5%) | 10 (6.8%) |
|  High (>21 [M], >14 [W]) | 21 (10.5%) | 2 (1.4%) |
|  |  |  |  |
| Number of systems medicated | 1.0 (0.0, 2.0) | 1.0 (1.0, 2.0) | 347 |
| Cortisol (ng/ml) | 110.0 (85.0, 139.2) | 100.3 (76.4, 126.6) | 347 |
| DHEAS (ng/ml) | 862.9 (670.8, 1143.9) | 577.5 (306.7, 886.3) | 347 |
| Cortisol:DHEAS ratio | 0.1 (0.1, 0.2) | 0.2 (0.1, 0.4) | 347 |
| IL-1β (pg/ml) | 11.3 (5.6, 17.7) | 16.3 (11.7, 26.9) | 252 |
| IL-6 (pg/ml) | 0.92 (0.24, 1.98) | 0.89 (0.40, 2.36) | 215 |
| IL-10 (pg/ml) | 2.9 (2.5, 4.7) | 1.9 (0.3, 2.1) | 268 |
| TNFα (pg/ml) | 0.8 (0.3, 1.1) | 0.6 (0.5, 1.4) | 248 |
| CRP (mg/l) | 2.0 (1.0, 4.1) | 3.1 (1.1, 5.7) | 340 |
|  |  |  |  |
| ***Annual change (%)*** |  |  |  |
| Cortisol | 1.4 (-1.0, 5.5) | 2.5 (-1.1, 8.3) | 262 |
| DHEAS | -2.5 (-5.2, 0.4) | -1.2 (-5.0, 3.1) | 258 |
| Cortisol:DHEAS ratio | 7.2 (1.2, 18.9) | 4.7 (-2.3, 19.5) | 257 |
| IL-1β | 0.3 (-5.3, 4.6) | -4.2 (-6.5, 0.4) | 148 |
| IL-6 | 27.6 (5.9, 115.2) | 24.3 (0.3, 77.8) | 162 |
| IL-10 | -8.6 (-9.9, -4.0) | -4.3 (-9.0, 2.9) | 54 |
| TNFα | 27.7 (12.1, 117.6) | 69.2 (20.1, 221.1) | 110 |
| CRP | 3.7 (-5.4, 25.9) | 2.7 (-6.1, 11.8) | 255 |
|  |  |  |  |
| **Follow-up (2003/5)** |  |  |  |
| Follow-up time (years) | 9.5 (9.0, 9.8) | 9.1 (8.6, 9.4) | 347 |
| HAD depression score | 3.0 (1.0, 5.0) | 3.0 (1.0, 6.0) | 346 |
|  |  |  |  |
| HAD depression score |  |  |  |
|  0-7 Non-case | 179 (89.5%) | 127 (87.0%) |  |
|  8-10 Possible case | 14 (7.0%) | 17 (11.6%) | 346 |
|  11+ Probable case | 7 (3.5%) | 2 (1.4%) |  |
|  |  |  |  |
| High HAD depression scorea | 79 (39.5%) | 49 (33.6%) | 346 |
| SF-36 mental health score | 84.0 (72.0, 92.0) | 76.0 (64.0, 88.0) | 343 |
| Poor SF-36 mental healthb | 77 (38.9%) | 49 (33.8%) | 343 |
| M: Men; W: Women |  |  |  |
| Obs: Number of non-missing observations |  |  |
| HAD: Hospital anxiety and depression scale |  |  |
| a Score in the highest sex-specific third of the distribution |  |  |
| b Score in the lowest sex-specific third of the distribution |  |  |

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| **Table 2: Risk of high HAD depression and poor SF-36 mental health scores at follow-up per standard deviation difference in baseline biomarker** |
|  |  |  |  |  |
| **Biomarker** | **M** | **Men and women pooled and adjusted for sex**  | **Men** | **Women** |
| **High depression** | **Poor mental health** | **High depression** | **Poor mental health** | **High depression** | **Poor mental health** |
| **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| Cortisol | 1 | **0.75 (0.60,0.94)** | **0.01** | 0.98 (0.79,1.23) | 0.89 | 0.80 (0.60,1.08) | 0.15 | 1.16 (0.86,1.57) | 0.33 | **0.63 (0.43,0.93)** | **0.02** | 0.79 (0.55,1.14) | 0.21 |
| 2 | **0.77 (0.61,0.98)** | **0.03** | 1.01 (0.80,1.27) | 0.92 | 0.83 (0.61,1.13) | 0.24 | 1.19 (0.87,1.63) | 0.28 | **0.61 (0.41,0.91)** | **0.02** | 0.82 (0.56,1.18) | 0.28 |
| DHEAS | 1 | 0.94 (0.76,1.18) | 0.60 | 0.80 (0.64,1.00) | 0.05 | 1.03 (0.77,1.37) | 0.84 | **0.71 (0.53,0.97)** | **0.03** | 0.84 (0.59,1.19) | 0.32 | 0.91 (0.65,1.29) | 0.61 |
| 2 | 1.02 (0.81,1.28) | 0.87 | 0.85 (0.68,1.08) | 0.19 | 1.10 (0.81,1.49) | 0.53 | 0.74 (0.54,1.01) | 0.06 | 0.93 (0.64,1.36) | 0.70 | 1.03 (0.71,1.50) | 0.87 |
| Cortisol:DHEAS ratio | 1 | 0.92 (0.74,1.15) | 0.47 | 1.18 (0.95,1.47) | 0.14 | 0.86 (0.64,1.16) | 0.33 | **1.41 (1.04,1.90)** | **0.03** | 0.97 (0.68,1.37) | 0.84 | 0.96 (0.68,1.36) | 0.84 |
| 2 | 0.88 (0.69,1.11) | 0.26 | 1.13 (0.90,1.41) | 0.30 | 0.83 (0.61,1.13) | 0.24 | **1.38 (1.01,1.87)** | **0.04** | 0.86 (0.59,1.24) | 0.41 | 0.86 (0.60,1.25) | 0.44 |
| IL-1β | 1 | 0.97 (0.75,1.26) | 0.82 | 1.25 (0.96,1.64) | 0.10 | 0.74 (0.51,1.06) | 0.10 | 1.12 (0.80,1.58) | 0.50 | 1.46 (0.93,2.29) | 0.10 | 1.52 (0.97,2.38) | 0.07 |
| 2 | 0.93 (0.71,1.22) | 0.62 | 1.27 (0.97,1.67) | 0.08 | 0.73 (0.50,1.05) | 0.09 | 1.13 (0.80,1.59) | 0.49 | 1.41 (0.88,2.26) | 0.15 | 1.60 (0.99,2.59) | 0.06 |
| IL-6 | 1 | 1.02 (0.77,1.35) | 0.89 | 1.04 (0.78,1.38) | 0.79 | 1.09 (0.77,1.54) | 0.63 | 1.03 (0.72,1.47) | 0.89 | 0.88 (0.53,1.47) | 0.63 | 1.00 (0.61,1.64) | 0.99 |
| 2 | 0.97 (0.73,1.30) | 0.86 | 1.00 (0.74,1.36) | 0.99 | 1.08 (0.75,1.55) | 0.68 | 0.99 (0.68,1.46) | 0.98 | 0.74 (0.41,1.33) | 0.31 | 0.96 (0.56,1.65) | 0.89 |
| IL-10 | 1 | 0.93 (0.72,1.21) | 0.59 | 0.80 (0.60,1.06) | 0.12 | 0.95 (0.70,1.28) | 0.74 | 0.77 (0.55,1.08) | 0.13 | 0.76 (0.42,1.37) | 0.36 | 0.85 (0.49,1.48) | 0.56 |
| 2 | 0.94 (0.72,1.23) | 0.65 | 0.80 (0.60,1.08) | 0.14 | 0.89 (0.65,1.23) | 0.49 | 0.78 (0.55,1.10) | 0.16 | 0.94 (0.47,1.91) | 0.87 | 0.83 (0.45,1.54) | 0.55 |
| TNFα | 1 | 1.07 (0.83,1.38) | 0.62 | 0.94 (0.72,1.23) | 0.66 | 1.01 (0.74,1.39) | 0.95 | 0.96 (0.69,1.33) | 0.80 | 1.20 (0.77,1.86) | 0.42 | 0.92 (0.59,1.44) | 0.72 |
| 2 | 1.07 (0.82,1.40) | 0.59 | 0.96 (0.74,1.26) | 0.79 | 0.99 (0.71,1.39) | 0.96 | 0.97 (0.69,1.36) | 0.85 | 1.24 (0.79,1.95) | 0.36 | 0.92 (0.58,1.47) | 0.74 |
| CRP | 1 | 1.24 (0.98,1.55) | 0.07 | 1.18 (0.94,1.48) | 0.16 | 1.21 (0.90,1.62) | 0.20 | 1.00 (0.75,1.33) | 0.99 | 1.27 (0.87,1.83) | 0.21 | **1.56 (1.06,2.30)** | **0.02** |
| 2 | 1.09 (0.85,1.39) | 0.52 | 1.20 (0.94,1.53) | 0.14 | 1.05 (0.76,1.45) | 0.77 | 1.03 (0.75,1.41) | 0.84 | 1.10 (0.73,1.65) | 0.65 | **1.57 (1.04,2.38)** | **0.03** |
|  |
| M: Model; OR: Odds ratio; P: P-valueModel 1: Adjusted for age and follow-up timeModel 2: Additionally adjusted for BMI, smoking history, alcohol consumption and number of systems medicatedHigh depression scores were those in the highest sex-specific third of the distribution; poor mental health scores were those in the lowest sex-specific thirdSignificant associations (p<0.05) are highlighted in bold |

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| **Table 3: Risk of high HAD depression and poor SF-36 mental health scores at follow-up per standard deviation increase in biomarker from baseline to follow-up** |
|  |  |  |  |  |
| **Biomarker** | **M** | **Men and women pooled and adjusted for sex**  | **Men** | **Women** |
| **High depression** | **Poor mental health** | **High depression** | **Poor mental health** | **High depression** | **Poor mental health** |
| **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| Cortisol | 1 | 0.80 (0.61,1.04) | 0.10 | 0.97 (0.74,1.25) | 0.79 | **0.63 (0.44,0.92)** | **0.02** | 1.11 (0.80,1.54) | 0.52 | 1.11 (0.73,1.69) | 0.62 | 0.72 (0.46,1.14) | 0.17 |
| 2 | 0.82 (0.62,1.08) | 0.16 | 0.97 (0.74,1.26) | 0.80 | **0.66 (0.45,0.97)** | **0.03** | 1.10 (0.79,1.54) | 0.58 | 1.15 (0.74,1.78) | 0.54 | 0.72 (0.45,1.14) | 0.16 |
| DHEAS | 1 | 0.96 (0.74,1.25) | 0.77 | 1.07 (0.82,1.39) | 0.61 | 0.99 (0.71,1.38) | 0.95 | 0.92 (0.67,1.28) | 0.64 | 0.92 (0.61,1.39) | 0.70 | 1.40 (0.89,2.22) | 0.15 |
| 2 | 0.95 (0.73,1.24) | 0.72 | 1.06 (0.81,1.38) | 0.67 | 0.98 (0.70,1.38) | 0.92 | 0.92 (0.66,1.29) | 0.63 | 0.92 (0.59,1.41) | 0.69 | 1.38 (0.87,2.20) | 0.17 |
| Cortisol:DHEAS ratio | 1 | 0.98 (0.76,1.28) | 0.90 | 0.95 (0.73,1.23) | 0.67 | 0.88 (0.63,1.24) | 0.48 | 1.12 (0.81,1.56) | 0.49 | 1.16 (0.77,1.75) | 0.47 | 0.67 (0.42,1.08) | 0.10 |
| 2 | 1.01 (0.77,1.31) | 0.95 | 0.95 (0.72,1.23) | 0.68 | 0.91 (0.64,1.28) | 0.58 | 1.10 (0.79,1.54) | 0.57 | 1.19 (0.78,1.83) | 0.42 | 0.68 (0.42,1.10) | 0.11 |
| IL-1β | 1 | 0.90 (0.65,1.25) | 0.54 | 0.71 (0.49,1.01) | 0.06 | 1.14 (0.75,1.74) | 0.53 | 0.75 (0.49,1.15) | 0.19 | 0.57 (0.29,1.10) | 0.09 | 0.60 (0.30,1.20) | 0.15 |
| 2 | 0.87 (0.62,1.22) | 0.41 | 0.70 (0.49,1.01) | 0.06 | 1.13 (0.73,1.76) | 0.58 | 0.77 (0.50,1.20) | 0.26 | 0.53 (0.26,1.08) | 0.08 | 0.57 (0.28,1.15) | 0.12 |
| IL-6 | 1 | 1.05 (0.75,1.46) | 0.77 | 1.05 (0.75,1.48) | 0.76 | 0.97 (0.64,1.47) | 0.89 | 0.83 (0.55,1.25) | 0.37 | 1.19 (0.68,2.08) | 0.54 | 2.02 (0.99,4.12) | 0.05 |
| 2 | 1.07 (0.75,1.51) | 0.72 | 1.08 (0.77,1.51) | 0.67 | 0.92 (0.59,1.43) | 0.70 | 0.85 (0.55,1.30) | 0.46 | 1.32 (0.70,2.47) | 0.39 | **2.31 (1.06,5.05)** | **0.04** |
| TNFα | 1 | 0.76 (0.51,1.14) | 0.19 | 0.81 (0.54,1.20) | 0.30 | 0.75 (0.46,1.21) | 0.24 | 0.66 (0.40,1.08) | 0.10 | 0.86 (0.41,1.80) | 0.69 | 1.30 (0.59,2.84) | 0.51 |
| 2 | 0.81 (0.54,1.22) | 0.31 | 0.81 (0.54,1.22) | 0.32 | 0.82 (0.50,1.36) | 0.44 | 0.68 (0.40,1.14) | 0.14 | 0.83 (0.38,1.84) | 0.65 | 1.53 (0.64,3.65) | 0.34 |
| CRP | 1 | 1.01 (0.77,1.31) | 0.96 | 1.04 (0.80,1.36) | 0.76 | 1.23 (0.87,1.73) | 0.23 | 1.03 (0.74,1.43) | 0.86 | 0.72 (0.46,1.11) | 0.14 | 1.08 (0.68,1.71) | 0.74 |
|  | 2 | 0.95 (0.72,1.24) | 0.69 | 1.05 (0.80,1.37) | 0.74 | 1.10 (0.77,1.57) | 0.59 | 1.05 (0.74,1.48) | 0.80 | 0.68 (0.42,1.08) | 0.10 | 1.11 (0.69,1.77) | 0.68 |
|  |
| M: Model; OR: Odds ratio; P: P-valueModel 1: Adjusted for ageModel 2: Also adjusted for BMI, smoking history, alcohol consumption and number of systems medicatedHigh depression scores were those in the highest sex-specific third of the distribution; poor mental health scores were those in the lowest sex-specific thirdConditional changes in biomarkers were derived using a residual change approach and were independent of baseline valuesOdds ratios greater than one: longitudinal increases in biomarker were related to increased risk of outcome at follow-up |

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| **Supplementary Table 1: Spearman correlations between biomarkers at baseline among men and women** |  |
|  |  |  |  |  |  |  |  |
| **Men** | Cortisol | DHEAS | Cortisol:DHEAS ratio | IL-1β | IL-6 | IL-10 | TNFα |
| DHEAS | 0.15 |  |  |  |  |  |  |
| Cortisol:DHEAS ratio | 0.58 | -0.66 |  |  |  |  |  |
| IL-1β | 0.26 | 0.03 | 0.18 |  |  |  |  |
| IL-6 | -0.29 | -0.04 | -0.18 | -0.09 |  |  |  |
| IL-10 | 0.05 | 0.17 | -0.08 | -0.13 | 0.17 |  |  |
| TNFα | 0.11 | 0.11 | 0.02 | 0.50 | 0.06 | 0.47 |  |
| CRP | 0.02 | 0.10 | -0.02 | 0.02 | 0.13 | 0.09 | 0.04 |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| **Women** | Cortisol | DHEAS | Cortisol:DHEAS ratio | IL-1β | IL-6 | IL-10 | TNFα |
| DHEAS | -0.06 |  |  |  |  |  |  |
| Cortisol:DHEAS ratio | 0.52 | -0.86 |  |  |  |  |  |
| IL-1β | -0.11 | 0.01 | -0.07 |  |  |  |  |
| IL-6 | 0.05 | -0.17 | 0.22 | 0.05 |  |  |  |
| IL-10 | -0.17 | 0.17 | -0.24 | 0.27 | 0.08 |  |  |
| TNFα | -0.01 | 0.00 | -0.04 | 0.46 | 0.16 | 0.16 |  |
| CRP | 0.05 | 0.06 | -0.01 | 0.00 | 0.36 | -0.05 | -0.10 |